EVALUATION AND COMPARISON OF EFFICACY AND SAFETY OF ATORVASTATIN ALONE AND IN COMBINATION WITH FENOFIBRATE IN DYSLIPIDEMIA

Dissertation submitted to

THETAMIL NADUDR. M.G.R. MEDICAL UNIVERSITY,CHENNAI-32

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MASTER OF PHARMACYIN

PHARMACY PRACTICE

Submitted By

Reg.No.26113181

Under The GuidanceOf

Mr. N.Venkateswaramurthy,M.Pharm.,

DEPARTMENTOFPHARMACY PRACTICE

J.K.K. NATTRAJA COLLEGE OF PHARMACY

KOMARAPALAYAM– 638 183

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"Evaluation and Comparison of Efficacy and Safety of Atorvastatin alone and in combination with Fenofibrate in Dyslipidemia"** submitted by the student bearing [**Reg. No: 26113181]** to "**The Tamil Nadu Dr. M.G.R. Medical University**", Chennai, in partial fulfillment for the award of Degree of **Master of Pharmacy** in **Pharmacy Practice** was evaluated by us during the examination held on……..…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"Evaluation and Comparison of Efficacy and Safety of Atorvastatin alone and in combination with Fenofibrate in Dyslipidemia"** submitted to "**The Tamil Nadu Dr. M.G.R. Medical University**", Chennai, in partial fulfillment to the requirement for the award of Degree of **Master of Pharmacy** in **Pharmacy Practice**, is a bonafide work carried out by **Mrs. M. Akilandeshwari, [Reg.No.26113181]** during the academic year 2012-2013, under the guidance and supervision of **Mr. N. Venkateswaramurthy., M.Pharm.,** Professor and Head, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Komarapalayam.

Place: Komarapalayam
Date:

Dr. R. SambathKumar, M.Pharm., Ph.D.,
Professor & Principal,
J.K.K. Nattraja College of Pharmacy.
Komarapalayam-638 183.

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Mr.N. Venkateswaramurthy ,M.Pharm,
Professor&Head,
Department of Pharmacy Practice,
J.K.K.NattrajaCollegeofPharmacy,
Komarapalayam-638183,
Tamil Nadu**.**

DECLARATION

I do here by declared that the dissertation entitled **"Evaluation and Comparison of Efficacy and Safety of Atorvastatin alone and in combination with Fenofibrate in Dyslipidemia"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University"**, Chennai, for the partial fulfillment of the degree of **Master of Pharmacy** in **Pharmacy Practice,** is a bonafide research work has been carried out by me during the academic year 2012-2013, under the guidance and supervision of **Mr. N. Venkateswaramurthy, M.Pharm.,** Professor & Head, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy , Komarapalayam .

I further declare that, this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place : Komarapalayam **M. Akilandeshwari,**

Date: **Reg. No.26113181.**

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M. Akilandeshwari.

Reg.No:26113181

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ABBREVIATIONS

HDL-C	High-density lipoprotein-cholesterol
LDL-C	Low-density lipoprotein-cholesterol
VLDL-C	Very low-density lipoprotein-cholesterol
IDL-C	Intermediate-Indensity lipoprotein-cholesterol
TC	Total cholesterol
TG_S	Triglycerides
Apo	Apolipoprotien
CE	Cholesterol ester
CETP	Cholesterol ester transfer protein
FC	Free cholesterol
LCAT	Lecithin- cholesterol acyltransferase
LPL	Lipoprotien lipase
NEFA	Non esterified fatty acids
HMG-CoA	Hydroxymethylglutaryl-coenzyme A
CHD	Coronary heart disease
MI	Myocardial infarction
TSH	Thyroid-stimulating hormone
DM	Diabetes mellitus
HTN	Hypertension
GFR	Glomerular filtration rate
CAD	Coronary artery disease
BMI	Body mass index
NCEP	National Cholesterol Educational Program
FDA	Food and drug administration
CVD	Cardiovascular disease
HIV	Human Immunodeficiency Virus
ACS	Acute coronary syndrome
mg	Milligram
kg	Kilogram
g	Gram
ug/mL	Microgram per mole
mg/mL	Milligram per mole
mg/dl	Milligram per deciliter
%	Percentage
SD	Standard deviation

INTRODUCTION

DYSLIPIDEMIA

Dyslipidemia means an abnormal amount of lipids, or fats, in the blood. Lipids are essential to life, but an excess of certain lipids can increase the risk for cardiovascular disease.Disorders of the metabolism of lipoproteins including lipoprotein over-production and deficiency are classified as Dyslipidemias.

The lipids that are commonly measured in blood include various forms of cholesterol, as well as triglycerides. High-density lipoprotein (HDL) is the "good cholesterol," and higher levels reduce the risk of cardiovascular disease. Low-density lipoprotein (LDL) is the "bad cholesterol," linked to increased risk of heart attacks and strokes. High triglycerides are also a risk factor for cardiovascular disease.

In dyslipidemia, the level of one or more of these lipids is abnormal (either too high or too low). Increased activity and a healthy diet should be the first course of treatment for dyslipidemia. If you are at risk for heart attack or stroke, and diet and exercise fail to bring high lipid levels into the healthy range, your doctor may recommend taking a lipid-lowering medicine

CLASSIFICATIONS OF DYSLIPIDEMIA

- **Primary Dyslipidemia**

These can be familial or genetic due to single gene effect or multiple genetic, dietary and physical activity related causes.

- **Secondary Dyslipidemia**

These forms of Dyslipidemia are a consequence of other conditions such as associated diseases and use of drugs.

EPIDEMIOLIGY

Coronary heart disease (CHD) is one of the primary causes of morbidity and mortality in Western countries.[1] Every year, 7.2 million people die from CHD worldwide, more than from

cancer or infectious causes. In the United States alone, 640,000 deaths can be attributed to CHD.[2]

Main causes of Dyslipidemia are.

- Genetic predisposition (tendencies to run in families)
- Diabetes
- Obesity
- Sedentary life styles
- Fatty food consumption
- Hypothyroidism (deficiency state of thyroid gland)
- Hyperhomocystinemia (increased levels of homocystine levels in blood)
- Smoking and Alcohol intake

What affects cholesterol levels?

A variety of things can affect cholesterol levels. These are things you can do something about:

Diet:

- Saturated fat and cholesterol in the food you eat make your blood cholesterol level go up.
- Saturated fat is the main culprit, but cholesterol in food also matters.
- Reducing the amount of saturated fats and cholesterol in diet helps lower your blood cholesterol levels.

Weight:

- Being overweight is a risk factor for heart disease.
- It also tends to increase your cholesterol.
- Losing weight can help lower L and total cholesterol levels, well as raise your HDL and lower your triglyceride levels.

Physical activity:

- Not being physically active is a risk factor for heart disease.

- Regular physical activity can help lower LDL (bad) cholesterol and raise HDL (good) cholesterol levels.
- It also helps you lose weight.
- You should try to be physically active 30 minutes on most, if not all days.

Age and Gender:

- As women and men get older, there cholesterol levels rise.
- Before the age of menopause, women have lower total cholesterol levels than men of same age.
- After the age of menopause, women's LDL levels tend to rise.

Heredity:

- Your genes partly determine how much cholesterol your body makes.
- High blood cholesterol can run in families.[3]

PATHOPHYSIOLOGY OF DYSLIPIDEMIA

The response to injury hypothesis states that risk factors such as

- oxidized LDL
- mechanical injury to the endothelium,
- excessive homocystien,
- immunologic attack or
- infection-induced changes in endothelial and intimal function lead to endothelial dysfunction and a series of cellular interactions

Cholesterol Homeostasis

Cholesterol is a lipid that serves primarily as a precursor to steroid hormones and bile acids, and as the main component of cell membranes. Sources of cholesterol needed to carry out normal life functions are manufactured by the body and ingested from exogenous dietary sources. Cholesterol levels in the blood reflect approximately 40% to 60% endogenous cholesterol, with the balance coming from dietary sources. Triglycerides, which are composed of fatty acids esterified to glycerol and used as energy substrates, are supplied by fats in the diet and through the conversion of carbohydrates by the liver.

Cholesterol, triglycerides, and other lipids in the body are transported through the bloodstream in spherical particles called lipoproteins. Lipoproteins can be divided into five major categories depending on their composition. The classes from largest and least dense to smallest and most dense are chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). The larger, more buoyant particles primarily have a triglyceride-rich core, while the smaller, more dense particles have a cholesterol ester core.[4] LDL accounts for approximately 60% to 70% of total serum cholesterol and is the primary atherogenic class of lipoproteins. HDL constitutes approximately 20% to 30% of total serum cholesterol with VLDL comprising about 10% to 15%.[5],[6]

Cholesterol/Lipoprotein Classes

Total Cholesterol: This represents the total serum cholesterol.

Triglycerides (TGs): Lipids carried through the bloodstream to tissues. Most of the body's fat tissue is in the form oftriglycerides, stored for use as energy. Triglycerides are obtained primarily from fat in foods.

Chylomicrons: A small fat globule composed of protein and lipid (fat). Chylomicrons are found in the blood and lymphaticfluid where they serve to transport fat from its port of entry in the intestine to the liver and to adipose tissue.

Very low density lipoproteins (VLDLs): Lipoproteins that are rich in triglycerides, produced in

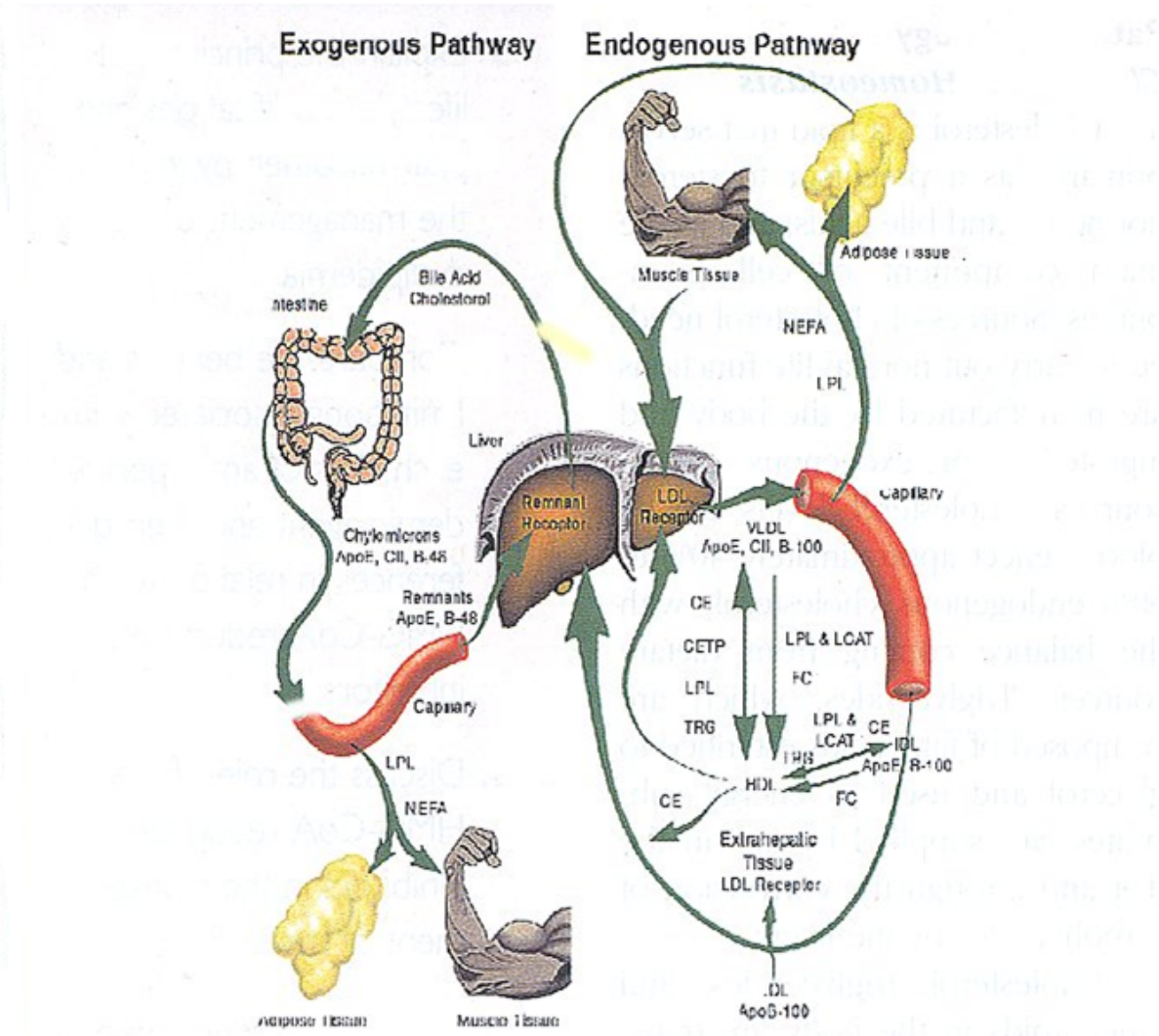
the liver, and are the majorcarriers of endogenous (produced by the body) triglycerides

Low-density lipoproteins (LDL): The final-stage lipoprotein from the catabolism of VLDLs. LDLs is the primary carrier ofcholesterol in the body. Intermediate density lipoproteins (IDL) are a subfraction of LDLs. LDLs are commonly knownas the ‘‘bad’’ cholesterol because they contribute to the buildup of plaque within the arteries. There are 7 different sizesof LDLs. The smaller, denser LDLs are more atherogenic.

High-density lipoproteins (HDL): HDLs are composed of a high proportion of protein with little triglyceride andcholesterol. HDLs are involved in reverse cholesterol transport, which is believed to protect against heart disease and stroke. HDLs are commonly known as the ‘‘good’’ cholesterol because they help keep cholesterol from building up inthe arteries. There are different subfractions of HDLs: HDL2 and HDL3. HDL2 is the subfraction that appears to beprotective against heart disease.[7]

Cholesterol is derived from two sources: exogenously from the systemic circulation and endogenously via intracellular synthesis.[8],[9] The exogenous lipoprotein system is responsible for the synthesis, transportation, and catabolism of chylomicron particles and remnants.Saturated, monounsaturated, and polyunsaturated fats and cholesterol esters digested and absorbed in the proximal small bowel are reformulated and packaged into chylomicrons by cells in the intestinal endothelium.Thus, chylomicrons are primarily composed of fatty acids, cholesterol, and apolipoproteins that are obtained from the diet. These chylomicrons then enter the lymphatic system and travel through the body until they are broken down by the enzyme lipoprotein lipase in the capillary beds to chylomicron remnants, which are smaller, contain less fatty acids, but have retained apolipoproteins B-48 and E. These remnants are then cleared from the circulation by the LDL-related receptor protein found in the liver.

Cholesterol homeostasis and transport in humans. Schematic for the endogenous and exogenous pathways of cholesterol synthesis and transport.



Apo = apolipoprotein; CE = cholesteryl ester; CETP = cholesteryl ester transfer protein; FC = free cholesterol; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LCAT = lecithin-cholesterol acyltransferase; LPL = lipoprotein lipase; NEFA = nonesterified fatty acids; TRG = triglycerides; VLDL = very-low-density lipoprotein. Adapted with permission from The American College of Clinical Pharmacy, Kansas City, MO.[7]

FIGURE:1

In addition to replenishing their cholesterol pools by taking up circulating lipoproteins from exogenous sources, cells can also synthesize their own cholesterol through the endogenous pathway. The intracellular synthesis of cholesterol involves a series of biochemical reactions starting with acetyl-CoA. The rate-limiting enzymes involved in this process are HMG-CoA synthetase, which catalyzes the conversion of acetyl- CoA to HMG-CoA, and HMG-CoA reductase, which catalyzes the conversion of hepatic HMG-CoA to mevalonic acid, used in a later step in the biosynthesis of cholesterol. The statins, or HMG-CoA reductase inhibitors, competitively inhibit this enzyme, reducing the capacity of the cell to synthesize cholesterol.[10]

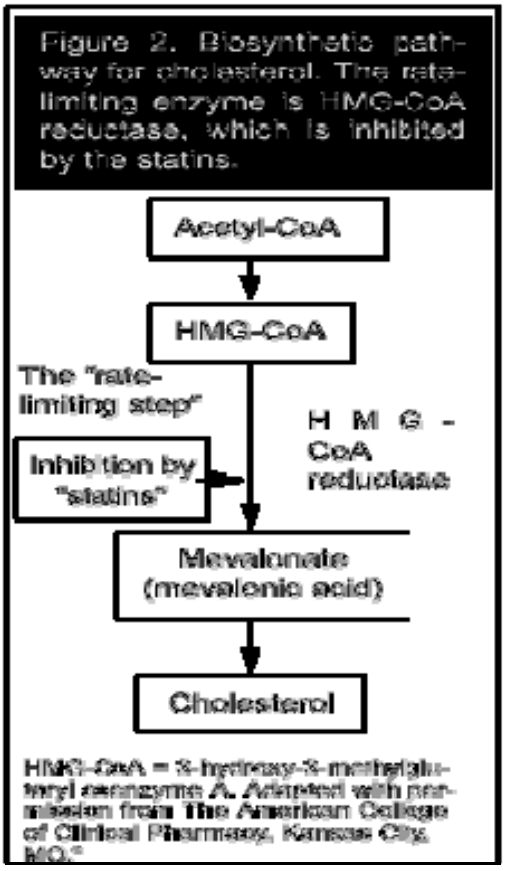


FIGURE:2

Fatty acids and cholesterol produced by the body are then transported through the endogenous pathway. Three major lipoproteins are involved in this pathway: VLDL, LDL, HDL. Triglycerides can be synthesized by the liver, especially in the presence of excess carbohydrates, and later secreted into the bloodstream as VLDL. These VLDL particles contain approximately five times more triglycerides than cholesterol, and also contain apolipoproteins B-100, E, and C-II. The B and E proteins link with B-E or LDL cell surface receptors, while apolipoprotein C-II functions as a cofactor for the enzyme lipoprotein lipase. Once secreted into the bloodstream, triglyceride molecules are hydrolyzed from the VLDL particles by lipoprotein lipase, located in the capillary beds. On release, these free fatty acids are used for energy production primarily by heart and skeletal muscle, or stored in fat cells. Nonetheless, this process of lipolysis decreases the triglyceride content and size of the VLDL particles, preparing them for either of their two known metabolic fates: clearance via the hepatic remnant receptor, or further release of triglycerides resulting in the formation of IDL particles.

IDL particles are high in triglyceride content, and contain almost all of the cholesterol initially contained in the VLDL particles. Lipolysis continues through the actions of lipoprotein lipase and hepatic lipase, leading to much smaller, cholesterol-rich LDL particles. By this time, apolipoproteins E and C have been removed, leaving only apolipoprotein B-100 on the LDL particles. IDL particles are intermediate products between VLDL and LDL particles and therefore have a short life span. Their cholesterol and triglyceride contents do not significantly impact cholesterol measurements. Except for rare dyslipidemias, less than 5% of cholesterol circulates in IDL particles. Half of these IDL particles are cleared from the circulation by the LDL receptor while the other half is converted to LDL particles.

LDL is the primary atherogenic lipoprotein, and the smaller the size of the LDL particle, the more it is able to penetrate into subendothelial tissue, where it contributes to the development of atherosclerosis. Excessive circulating LDL cholesterol will cause cholesterol deposition outside of the cell, causing atherogenic plaque formation in the vascular endothelium, potentially leading to coronary artery disease (CAD).Two specific types of LDL particles have recently been identified to be highly associated with HD risk. The first, a lipoprotein(a) [Lp(a)] particle, is a very small LDL particle surrounded by a plasminogen-like protein. The other subclass of small, dense LDL particles is referred to as atherogenic lipoprotein phenotype B. This subclass is found

in approximately 30% of the population and is associated with a high risk of CHD.

The third major lipoprotein involved in the endogenous pathway is HDL. Similar to LDL particles, HDL particles are rich in cholesterol and very small. However, HDL particles appear to be involved in reverse cholesterol transport, resulting in an antiatherogenic effect. Specifically, HDL may prevent or remove cholesterol deposits within the arterial wall. Other possible explanations for the beneficial role of HDL cholesterol include the following:

1) prevents LDL oxidation by working as an antioxidant
2) reduces platelet aggregability by increasing prostacyclin production
3) stabilizes serum prostacyclin and promotes fibrinolysis
4) competitively inhibits the uptake of LDL by endothelial cells
5) prevents LDL aggregation and uptake by macrophages
6) decreases cholesterol and foam cell formation
7) inhibits platelet activation by LDL through the phosphatidylinositol cycle.

An important function of HDL is that it can serve as a marker for abnormal metabolism of chylomicrons and VLDL particles, because as triglycerides increase, HDL decreases.

Two key enzymes are involved in the transport of cholesterol from the periphery to the liver, where it can be eliminated by HDL particles. Lecithin-cholesterol acyltransferase is responsible for converting the cholesterol in HDL particles into insoluble cholesterol esters, causing them to partition in the core of these lipoproteins. The other enzyme, cholesterol ester transfer protein, is involved in the transfer of cholesterol esters from HDL particles to triglyceride-rich particles in exchange for triglyceride molecules. Once in VLDL and IDL particles, cholesterol is transported to the liver for elimination.

All three lipoproteins are highly involved in the transport of triglycerides and cholesterol from the liver to the body where they may be used by cells, and from the body to the liver where they may be eliminated. If the amount of cholesterol is insufficient to meet the requirements of any cell, the cell will up-regulate its synthesis of the LDL receptor. The newly formed LDL receptor will migrate to an area on the surface of the cell called the coated pits. Once in the coated pits, the cell is capable of recognizing circulating lipoproteins that contain either

apolipoprotein E or B (VLDL, IDL, and LDL particles). Both the VLDL and IDL particles contain both B and E proteins and therefore may have a higher binding affinity for the LDL receptor than the LDL particles. Once binding occurs, the lipoproteins are internalized by the cell, taken up by liposomes, and broken down into elemental substances to be used by the cell. The LDL receptor protein returns to the cell surface where it can bind with another circulating lipoprotein, repeating the process again.

Link Between Cholesterol and CHD

The processes by which lipids and lipoproteins participate in atherosclerotic plaque formation and CHD events continue to be an area of controversy and research. One of the initiating events of atherosclerotic plaque formation appears to be the entrance of lipoproteins LDL and Lp(a) into the subendothelial space with their oxidatively modified free radicals produced by smooth muscle cells, activated macrophages, and endothelial cells. These oxidatively modified lipoproteins enter macrophages through a scavenger receptor pathway, ultimately yielding lipid-rich foam cells. Circulating monocytes are also attracted to smooth muscle and endothelial cells by chemoattractant that is augmented by the oxidatively modified lipoproteins.

As the macrophage scavenger receptor continues to uptake oxidatively modified lipoproteins, foam cells continue to form and progress to the next level of atherogenesis, which is the formation of the fatty streak. At the same time, smooth muscle cells migrate into the subendothelial space and begin proliferating within the intima, contributing to the overall atherogenic process. As the process continues, lesions continue to grow by increased smooth muscle cell proliferation and collagen synthesis. At this point, necrosis of the foam cell and formation of an extracellular lipid core occurs, as long as plasma LDL levels are elevated. The final phase appears to involve an autoimmune inflammatory response that causes T lymphocyte infiltration of the adventitia (the outermostconnective tissue covering of a vessel). This inflammatory response appears to complete the process of plaque formation that is the underlying culprit in CHD.

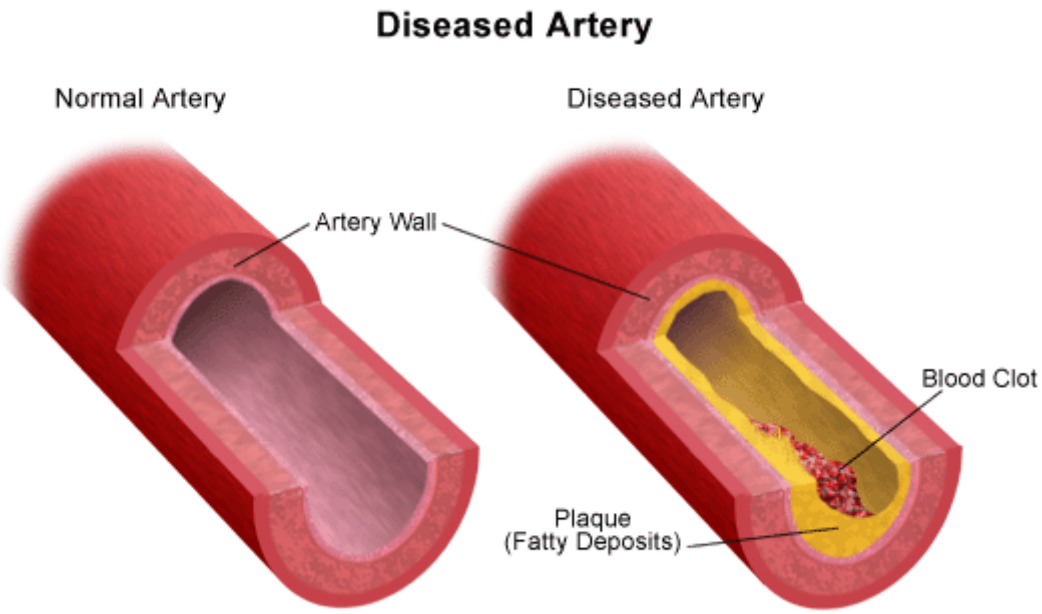


FIGURE:3

National Cholesterol Educational Program Guidelines

- **Total cholesterol**

<200mg/dL	Desirable
200-239mg/dL	Borderline high
≥240mg/dL	High

- **High Density Lipoprotiens**

<40mg/dL	Low
>60mg/dL	High

- **Low Density Lipoprotiens**

<100mg/dL	Optimal
100-129mg/dL	Near optimal
130-159mg/dL	Borderline high

160-189mg/dL	High
>190mg/dL	Very high

- **Triglycerides**

<150mg/dL	Normal
150-199mg/dL	Borderline high
200-499mg/dL	High
≥500mg/dL	Very high

Signs and Symptoms

- Dyslipidemia itself usually causes no symptoms.[11]
- Serum lipid levels should be monitored regularly.[12],[13]

Dyslipidemia can increase the risk of coronary artery disease (CAD) and peripheral arterial disease.[14]

- Symptoms of CAD include angina and dyspnoea.[15]
- Symptoms of peripheral arterial disease include intermittent claudication (pain, numbness, aching, or heaviness in the leg muscles during movement and/or cramping in the legs, buttocks, thighs, calves, or feet).[16]
- However, both conditions may also be asymptomatic.

Very high levels of triglycerides (>11.29 mmol/L [>1000 mg/dL]) are a known but rare cause of pancreatitis in the general population.[17]

- The initial sign of acute pancreatitis is gradual or sudden pain in the upper abdomen that sometimes extends through to the back.
- Other symptoms may include a swollen and tender abdomen, nausea and vomiting, fever, and tachycardia.[18]

Diagnosis

- Serum lipid profile (measured total cholesterol, TG, and HDL cholesterol and calculated LDL cholesterol and VLDL.

Dyslipidemia is suspected in patients with characteristic physical findings or complications of dyslipidemia (eg, atherosclerotic disease). Primary lipid disorders are suspected when patients have physical signs of dyslipidemia, onset of premature atherosclerotic disease (at < 60 yr), a family history of atherosclerotic disease, or serum cholesterol > 240 mg/dL (> 6.2 mmol/L). Dyslipidemia is diagnosed by measuring serum lipids. Routine measurements (lipid profile) include total cholesterol (TC), TGs, HDL cholesterol, and LDL cholesterol.

Lipid profile measurement: TC, TGs, and HDL cholesterol are measured directly; TC and TG values reflect cholesterol and TGs in all circulating lipoproteins, including chylomicrons, VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL. TC values vary by 10% and TGs by up to 25% day-to-day even in the absence of a disorder. TC and HDL cholesterol can be measured in the nonfasting state, but most patients should have all lipids measured while fasting for maximum accuracy and consistency.

Testing should be postponed until after resolution of acute illness, because TGs increase and cholesterol levels decrease in inflammatory states. Lipid profiles can vary for about 30 days after an acute MI; however, results obtained within 24 h after MI are usually reliable enough to guide initial lipid-lowering therapy.

LDL cholesterol values are most often calculated as the amount of cholesterol not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5 because the cholesterol concentration in VLDL particles is usually $^1/_5$ of the total lipid in the particle. Thus, LDL cholesterol = TC − [HDL cholesterol + (TGs ÷ 5)] (Friedewald formula). This calculation is valid only when TGs are < 400 mg/dL and patients are fasting, because eating increases TGs. The calculated LDL cholesterol value incorporates measures of all non-HDL, nonchylomicron cholesterol, including that in IDL and lipoprotein (a) [Lp(a)]. LDL can also be measured directly using plasma ultracentrifugation, which separates chylomicrons and VLDL fractions from HDL and LDL, and by an immunoassay method. Direct measurement may be useful in some patients

with elevated TGs, but these direct measurements are not routinely necessary. The role of apo B testing is under study because values reflect all non-HDL cholesterol (in VLDL, VLDL remnants, IDL, and LDL) and may be more predictive of CAD risk than LDL alone.

Other tests: Patients with premature atherosclerotic cardiovascular disease, cardiovascular disease with normal or near-normal lipid levels, or high LDL levels refractory to drug therapy should probably have Lp(a) levels measured. Lp(a) levels may also be directly measured in patients with borderline high LDL cholesterol levels to determine whether drug therapy is warranted. C-reactive protein and homocysteine measurement may be considered in the same populations.

Tests for secondary causes of dyslipidemia—including measurements of fasting glucose, liver enzymes, creatinine, thyroid-stimulating hormone (TSH), and urinary protein—should be done in most patients with newly diagnosed dyslipidemia and when a component of the lipid profile has inexplicably changed for the worse.

Screening: A fasting lipid profile (TC, TGs, HDL cholesterol, and calculated LDL cholesterol) should be obtained in all adults ≥ 20 yr and should be repeated every 5 yr. Lipid measurement should be accompanied by assessment of other cardiovascular risk factors, defined as

- Diabetes mellitus
- Cigarette use
- Hypertension
- Family history of CAD in a male 1st-degree relative before age 55 or a female 1st-degree relative before age 65

A definite age after which patients no longer require screening has not been established, but evidence supports screening of patients into their 80s, especially in the presence of atherosclerotic cardiovascular disease.

Indications for screening patients < 20 yr are atherosclerotic risk factors, such as diabetes, hypertension, cigarette smoking, and obesity; premature CAD in a parent, grandparent, or sibling; or a cholesterol level > 240 mg/dL (> 6.2 mmol/L) or known dyslipidemia in a parent. If

information on relatives is unavailable, as in the case of adopted children, screening is at the discretion of the health care practitioner.

Patients with an extensive family history of heart disease should also be screened by measuring Lp(a) levels.[19]

Screening Recommendations - full fasting lipid profile

Men	All men ≥ 40 years every 1 - 3 years
Women	All women postmenopausal and/or ≥ 50 years every 1 – 3 years
Children	Family history of severe hypercholesterolemia or chylomicronemia
Adults (≥ 18 years)	All adults at any age with the following additional risk factors or at the discretion of physician • Exertional chest discomfort, dyspnea, or erectile dysfunction • Cigarette smoking - current or within past year • Abdominal obesity - waist: men > 102 cm or women > 88 cm (lower cut-offs are appropriate in South & East Asians) • Family history of premature coronary artery disease (CAD) • Manifestations of hyperlipidemia e.g., xanthelasma, xanthoma, corneal arcus • Diabetes mellitus (DM) • Hypertension (HTN) • Chronic kidney disease GFR < 30 mL/min/1.73m2 • Systemic lupus erythematosus • Evidence of atherosclerosis

Management

Nonpharmacologic Treatment

Lifestyle

Smoking Cessation	Results in a 36% reduction in the relative risk of mortality from CAD.
Diet	↓ saturated and trans fats ↓ simple sugars and refined carbohydrates ↑ fruits and vegetables ↑ whole-grain cereals ↑ proportion of mono- and polyunsaturated oils, including omega-3 fatty acids
Optimal Waist Circumference	< 94 cm (37 in) for men < 80 cm (32 in) for women Differs by ethnicity with lower cut-offs appropriate for South and East Asians.
Optimal BMI	< 25 kg/m^2
Exercise	30 min. daily moderate physical activity[20]

Initiation of drug therapy should be considered after 6 months of lifestyle modification. Although drug therapy is started, lifestyle modifications should be continued to enhance pharmacotherapy. In patients with severe dyslipidemia where the clinician does not feel that lipid levels will be normalized through diet alone, pharmacologic treatment may be initiated sooner. Clinical assessments of patients must be individualized even if it means deviating from the standard guidelines set by the NCEP.[21]

PHARMACOLOGICAL MANAGEMENT:

HMG-Co A Reductase Inhibitors

- Atorvastatin, Simvastatin, Lovastatin, Pravastatin and Rosuvastatin**.**

Bile Acid Binding Resins

- Cholestyramine, Colestipol and Colesevelam

Activators of Lipoprotein Lipase

- Gemfibrozil, Bezofibrate and Fenofibrate

Inhibitors of lipolysis and triglyceride synthesis

- Niacin

Inhibitor of Intestinal Absorption of Cholesterol

- Ezetimibe and Gugulipid.

HMG-CoA Reductase Inhibitors ("Statins")

The statins, or HMG-CoA reductase inhibitors, have taken a major role in the management of dyslipidemia, especially in the treatment of elevated LDL cholesterol. More specifically, this family of agents is considered first line for the treatment of hypercholesterolemia in patients who have failed to adequately respond to dietary therapy.There are currently six FDA-approved HMG-CoA reductase inhibitors marketed in the United States. They all work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in the biosynthesis of cholesterol. After administration, the HMG-CoA reductase inhibitors concentrate in the liver, the major site of cholesterol synthesis. All of the available HMG-CoA reductase inhibitors have the ability to decrease LDL and triglyceride levels, while increasing HDL cholesterol. Their main differences lie in their pharmacokinetic profiles, the amount of lipoprotein alterations, and cost. The statins are well tolerated, and there does not appear to be major differences in toxicity or adverse-effect profiles.

The HMG-CoA reductase inhibitors are currently used as adjuncts to diet therapy and in combination with other lipid-altering agents. They are also important in the treatment of dyslipidemia in patients with other comorbid conditions, such as diabetes. Experts have defined the ideal HMG-CoA reductase inhibitor as one that is well absorbed, reaches the liver unchanged, undergoes complete hepatic transformation, and is excreted via the hepatobiliary system. In addition, their once-daily dosing intervals, high efficacy, and tolerability with a low potential for drug interactions are other important criteria.[22] Of the six statins currently available, slight differences among them help determine the selection of the most appropriate statin for each patient.

Bile-Acid Sequestrants/Resins

Cholestyramine (Questran) and colestipol (Colestid) are bile-acid–binding resins indicated for the treatment of hypercholesterolemia. These agents exchange an anion, usually sodium, for bile acids in the intestinal tract, forming a nonabsorbable complex. This interrupts the recycling of bile acids through the enterohepatic circulation, stimulating hepatic cells to convert more of the cholesterol pool into bile acids. Up-regulation of the B-E/LDL receptor occurs, enhancing the uptake of circulating lipoproteins by hepatic cells, thereby reducing the concentration of cholesterol.

Bile-acid sequestrants primarily affect LDL particles, causing an average 15% to 27% reduction in total and LDL cholesterol at high doses, and 10% to 23% reduction with 1 to 3 packets or scoops per day. The decrease in LDL appears to reduce the cholesterol content and the size of the LDL particles. A 7- to 10-year, double-blind, randomized trial compared the effects of diet plus cholestyramine with diet plus placebo in 3,806 men without known CHD but an elevated cholesterol level of at least 265 mg/dL. The occurrence of nonfatal myocardial infarction or death from CHD was 8.6% in the placebo group as opposed to 7% in the cholestyramine group, a statistically significant difference.[23] Unfortunately however, resin therapy tends to raise triglyceride concentrations about 7% in the short term, and 2% to 3% after prolonged therapy.Thus, they should be avoided in patients with mixed lipid disorders.

Cholestyramine and colestipol should be initiated with 1 to 2 doses (packets or scoops)

per day, taken anytime without regard to meals. For additional reductions in cholesterol, 4 to 6 packets or scoops may be taken daily. However, most patients cannot tolerate a full therapeutic dose and usually achieve a significant reduction in cholesterol with 2 to 4 packs per day. Compliance with the resins is usually less than 50% because of inconvenience and gastrointestinal distress. Doses can be taken all at once for convenience, but divided doses are recommended to reduce gastrointestinal effects caused by increased bulk. The most common adverse effects involve the gastrointestinal tract and include abdominal pain, belching, bloating, gas, constipation, nausea, and heartburn. These side effects can be reduced by slowly titrating dosages so that the patient can accommodate to each dosage, or have the patient increase the intake of soluble fiber either with dietary changes or supplemental compounds.

The bile-acid sequestrants have the advantage of low toxicity, no systemic drug-drug interactions, and complementary effects on lipoprotein metabolism when added to other hypolipidemic agents. One should always remember to separate the time of resin administration from that of other drugs by approximately 2 hours because of the potential for the other drug to adsorb onto the resin.

Fibric-Acid Derivatives/Fibrates

Currently, three fibrates are approved for use in the United States: clofibrate (Atromid-S), gemfibrozil (Lopid), and fenofibrate (Tricor). Fibrates primarily lower triglycerides by increasing the activity of lipoprotein lipase, which is responsible for the hydrolysis of triglycerides from VLDL to LDL particles. If the concentration of triglyceride-rich VLDL particles is elevated, rapid conversion to smaller IDL and LDL particles by lipoprotein lipase may overwhelm the system and cause an increase in LDL cholesterol. However, in individuals with normal to modestly elevated triglycerides, fibrates may produce a modest reduction in LDL cholesterol. In addition, fibric-acid derivatives offer the benefit of increasing HDL cholesterol. In the Helsinki Heart Study, a 5-year, double-blind, placebo-controlled trial, 4,081 asymptomatic men with hypercholesterolemia were randomly assigned to receive gemfibrozil600 mg twice daily or placebo. A 10% decrease in total cholesterol, 11% decrease in LDL cholesterol, and an 11% increase in HDL cholesterol occurred in patients treated with gemfibrozil, and was associated with a significant decrease in cardiac events after 5 years of treatment.[24]

Clofibrate is rarely used because of a study reporting an increased mortality with clofibrate use.[25]Gemfibrozil, however, is prescribed at a usual dose of 600 mg twice daily. Fenofibrate (Tricor) is the most recent FDA-approved fibric- acid derivative, offering 67 mg of micronized fenofibrate in each oral capsule. This newly micronized formulation should be initiated at a dose of 67 mg/day, taken once daily with a meal, and increased gradually to a maximum dose of 3 capsules/day (201 mg) when necessary after repeat serum triglyceride estimations at 4 to 8 weeks.[26] Although more direct comparisons are needed, fenofibrate may decrease LDL cholesterol more than gemfibrozil. Unfortunately, there are no data available on the effects of fenofibrate on CHD.[27]

Side effects of the fibrates include myalgias, elevated liver function tests, gastrointestinal discomfort, and rashes. The most severe side effect is the ability of the fibrates to increase cholesterol in the bile, which can lead to an increase in gallstone formation.

Niacin/Nicotinic Acid

Niacin (Niacor, Nicolar, niacin tablets) is an essential B vitamin that has lipid-regulating effects when administered at higher doses. The major mechanism of action appears to be the decreased release of VLDL, which in turn leads to decreased levels of IDL and LDL in the endogenous cascade.[10] In addition, niacin appears to reduce cholesterol concentrations through several mechanisms that include: reducing the hepatic synthesis of apolipoprotein B-containing particles, decreasing free fatty acid concentrations by inhibiting adipose tissue lipolysis, decreasing the synthesis of Lp(a), and decreasing the metabolism of HDL particles. Niacin has the advantage of increasing HDL cholesterol more than any other agent.[28] Niacin is approved for the treatment of hypertriglyceridemia, hypercholesterolemia, and mixed hyperlipidemias.

To effectively lower lipid levels, niacin should be administered at dosages of 1.5 to 6 grams/day. Niacin reduces both the size and quantity of VLDL particles produced by the liver, causing the concentration of triglycerides to fall by approximately 20% to 50%. In addition, niacin can decrease LDL cholesterol by 10% to 25%, and increase HDL cholesterol by 15% to 35%. In the Coronary Drug Project Research Group, a placebo-controlled trial conducted in men with previous myocardial infarction, total mortality in the niacin group was significantly reduced

by 11% at 15-year follow-up, which included almost 9 years after discontinuation of the study drug.[29],[30] Although it offers many benefits, the majority of patients receiving niacin experience one or more side effects, which include flushing, tingling, itching, rash, and headaches, which are thought to be produced by prostaglandin-mediated vasodilation. To lessen these side effects, the dosage should be titrated slowly. Patients are also advised to take niacin with food or with a dose of 325 mg of aspirin 30 minutes before taking the niacin to reduce the prostaglandin-mediated vasodilation. Other significant adverse effects that can occur from niacin therapy include dyspepsia, diarrhea, flatulence, and elevations in blood glucose and uric acid concentrations.

Niacin has also been available in a sustained-release formulation to reduce the dosing frequency. Sustained-release niacin has been associated with hepatotoxicity, but it appears to be associated almost exclusively with the older sustained-release formulations.[31] This hepatotoxicity appears to be dose-related, most often occurs at daily doses greater than 2 grams, and is completely reversible once the drug is discontinued.[32],[33]Several cases of fulminant hepatic failure have been reported in patients taking high-dose time-release niacin (>2 grams/day)[34],[35]. A recent randomized, double-blind, placebo-controlled trial of 223 hypercholesterolemic patients comparing the newer Niaspan versus plain niacin at a dose of 1.5 grams/day demonstrated no clinically significant hepatic dysfunction.[36] In addition, adverse reactions, including general malaise, anorexia, and jaundice, have been reported after an abrupt change from the immediate- to sustained-release formulation. The dosages of the sustained-release formulation that caused these adverse effects were well above the usual recommended daily dose of 0.25 to 1 gram. There is approximately a threefold to sixfold difference in the upper limits of the recommended dosages of the sustained-release formulation (1 gram/day) as opposed to the immediate-release formulation (3 to 6 grams/day), which may be attributable to the differences in metabolic handling of the two formulations. As mentioned previously, niacin can cause blood glucose levels to rise, and is known to increase uric acid concentrations with the potential of precipitating gout. In a recent double-blind, placebo-controlled trial of 223 patients with hypercholesterolemia, plain niacin increased fasting plasma glucose levels 4.8%, while Niaspan increased levels by 4.5%. However, uric acid levels increased less, 6% with Niaspan versus 16% with plain niacin, a statistically significant difference.[37]Although the results of this

study show that Niaspan may be safer for patients with other comorbid conditions, further studies are needed to evaluate if Niaspan offers any significant benefit over plain niacin for patients with diabetes or gout.

Niacin should be initiated at a dose of 100 mg twice daily for 1 week. If this is tolerated, the dose is increased to 200 mg twice daily for the following week. If the patient continues to tolerate the niacin, the dose is increased to 300 to 400 mg twice daily for 6 weeks. At this time, the patient should undergo a lipid profile and liver function tests prior to a clinic visit. If the patient continues to tolerate the niacin, and the lipid panel shows a positive response, the dosage is changed to 500 mg twice daily and the patient is reevaluated in 6 to 7 weeks.

Combination Therapy

Combination therapy is often necessary in severe cases of dyslipidemia. The introduction of higher potency statins, such as atorvastatin, has largely decreased the need for combination therapy to lower LDL levels. However, statins may be combined with a variety of other hypolipidemic agents to obtain a synergistic effect by using agents that work through different mechanisms of action. The most widely used combination regimen involves a statin and a bile-acid sequestrant, which has been shown to be safe, complementary, cost-effective, and valuable in severe hypercholesterolemia.[38],[39] The bile-acid sequestrant will interrupt the enterohepatic circulation of the cholesterol-rich bile salt pool, leading to increases in hepatic bile-acid synthesis and LDL receptor activity. Increased clearance of LDL from the circulation in conjunction with increased gastrointestinal loss of cholesterol will stimulate HMG-CoA reductase activity, increasing cholesterol synthesis and returning cholesterol levels to normal. This increased synthesis of cholesterol may be partially inhibited by combining a statin with the resin, resulting in an enhanced reduction in LDL.[40] In a recent meta-analysis, combination therapy with cholestyramine and a statin (fluvastatin, lovastatin, pravastatin, or simvastatin) produced decreases of 55% in LDL, 27% to 43% in total cholesterol, and 2% to 15% in triglycerides. In addition, these combinations increased HDL by 7% to 17%. Combination therapy with a statin and a resin can impact lipid levels more significantly than either agent alone.[41]

Statins have also been combined with fibric-acid derivatives that act primarily by increased

catabolism of triglyceride-rich lipoproteins by stimulating lipoprotein lipase, resulting in enhanced VLDL degradation. However, if there is also a receptor defect, the increased LDL generated as an end product may not be cleared from the circulation. Therefore, the combination of a fibrate and a statin may alleviate this effect. The controversial issue that remains to be addressed is whether these lipid-lowering benefits outweigh the potential risks of therapy. Both statins and fibric-acid derivatives have been linked individually to myopathy, and in combination, they can potentially accentuate this adverse event. However, the incidence of myopathy in patients taking the combination regimen is less than 1.0%.[42]Therefore, the combination of a fibrate and a statin may be used cautiously in patients with mixed lipid disorders, with a low risk of muscle necrosis. The regimen should be discontinued at the first sign of muscle ache.

The combination of niacin 1,500 to 3,000 mg with a statin further reduces LDL by 10% to 15%, triglycerides by 10% to 30%, and increases HDL by 9% to 12%. This combination has the added benefit of reducing atherogenicity by reducing particle size and postprandial remnant accumulation. There is a risk of hepatic necrosis and rhabdomyolysis using this combination, but with careful monitoring, the risk is quite low.[43]

Because atorvastatin has the most powerful LDL-lowering effect, with the added benefit of reducing triglycerides, combination therapy may not be necessary. Compliance is often a problem when patients are asked to take more medications, and the risk of drug interactions becomes an issue. Therefore, the treatment of dyslipidemia should always start with lifestyle modifications. If lipid-lowering responses are inadequate, then pharmacotherapy can be added to lifestyle modifications, but single drug therapy should always be maximized before the addition of a second agent to maximize compliance and minimize the chance of drug interactions and cost issues.

Currently Available Lipid-Lowering Medications

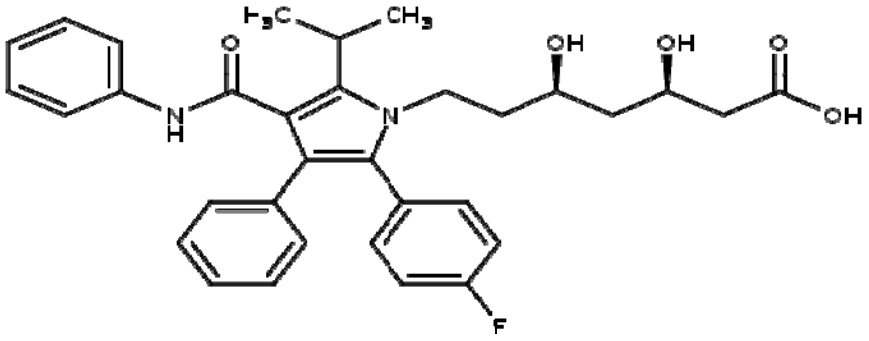
Generic Name	Trade Name (*generic available)	Dose
Statins		
Atorvastatin	Lipitor	10 mg - 80 mg
Fluvastatin	Lescol, LescolXL	20 mg - 80 mg
Lovastatin	Mevacor *	20 mg - 80 mg
Pravastatin	Pravachol *	10 mg - 80 mg
Rosuvastatin	Crestor	5 mg - 40 mg
Simvastatin	Zocor *	10 mg - 80 mg
Bile acid and/or cholesterol absorption inhibitors		
Cholestyramine	Questran*	2 g - 24 g
Colestipol	Colestid	5 g - 30 g
Ezetimibe	Ezetrol	10 mg
Fibrates		
Bezafibrate	Bezalip *	400 mg
Fenofibrate	Lipidil	
	-Micro*	67 mg, 200 mg
	-Supra*	100 mg, 160 mg
	-EZ	48 mg, 145mg
Gemfibrozil	Lopid *	600mg–1200mg
Niacins		
Nicotinic acid	Crystallineniacin*	1 g - 3 g
	Niaspan	0.5 g - 2 g

1.ATORVASTATIN

DESCRIPTION:

Atorvastatin (Lipitor) is a member of the drug class known as statins. It is used for lowering cholesterol. Atorvastatin is a competitive inhibitor of hydroxyl methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme in cholesterol biosynthesis via the mevalonate pathway. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate. Atorvastatin acts primarily in the liver. Decreased hepatic cholesterol levels increases hepatic uptake of cholesterol and reduces plasma cholesterol levels.

STRUCTURAL FORMULA



CHEMICAL NAME:

(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

MOLECULAR FORMULA:

$C_{33}H_{35}FN_2O_5$

MOLECULAR WEIGHT:

558.63

EXPERIMENTAL PROPERTIES:

Property	Value
melting point	159.2-160.7 °C
Water solubility	Sodium salt soluble in water, 20.4 ug/mL (pH 2.1), 1.23 mg/mL (pH 6.0)
LogP	5.7

CLINICAL PHARMACOLOGY:

Mechanism of action

Atorvastatin selectively and competitively inhibits the hepatic enzyme HMG-CoA reductase. As HMG-CoA reductase is responsible for converting HMG-CoA to mevalonate in the cholesterol biosynthesis pathway, this results in a subsequent decrease in hepatic cholesterol levels.Decreasedhepatic cholesterol levels stimulates upregulation of hepatic LDL-C receptors which increases hepatic uptake of LDL-C and reduces serum LDL-C concentrations.

Absorption:

Atorvastatin is rapidly absorbed after oral administration with maximum plasma concentrations achieved in 1 to 2 hours. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic bioavailability is due to presystemic clearance by gastrointestinal mucosa and first-pass metabolism in the liver.

Volume of distribution:

381 L

Protein binding:

>98% bound to plasma proteins

Route of elimination:

Eliminated primarily in bile after hepatic and/or extrahepaticmetabolism.Does not appear to undergo significant enterohepatic recirculation. Less than 2% of the orally administered dose is recovered in urine.

Pharmacodynamics:

Atorvastatin, a selective, competitive HMG-CoA reductase inhibitor, is used to lower serum total and LDL cholesterol, apoB, and triglyceride levels while increasing HDL cholesterol. High LDL-C, low HDL-C and high TG concentrations in the plasma are associated with increased risk of atherosclerosis and cardiovascular disease. The total cholesterol to HDL-C ratio is a strong predictor of coronary artery disease and high ratios are associated with higher risk of disease. Increased levels of HDL-C are associated with lower cardiovascular risk. By decreasing LDL-C and TG and increasing HDL-C, atorvastatin reduces the risk of cardiovascular morbidity and mortality. Atorvastatin has a unique structure, long half-life, and hepatic selectivity, explaining its greater LDL-lowering potency compared to other HMG-CoA reductase inhibitors.

Half life:

14 hours, but half-life of HMG-CoA inhibitor activity is 20-30 hours due to longer-lived active metabolites

Toxicity:

Generally well-tolerated. Side effects may include myalgia, constipation, asthenia, abdominal pain, and nausea. Other possible side effects include myotoxicity(myopathy,myositis, rhabdomyolysis) and hepatotoxicity. To avoid toxicity in Asian patients, lower doses should be considered.

DOSAGE FORMS:

Dosage forms	Route	strength
Tablet	Oral	10mg
Tablet	Oral	20mg
Tablet	Oral	40mg
Tablet	Oral	80mg

FOOD INTERACTION:

- Avoid alcohol.
- Avoid drastic changes in dietary habit.
- Avoid taking grapefruit or grapefruit juice throughout treatment. Grapefruit can significantly increase serum levels of this product.
- Food may decrease maximumplasma levels and area under the curve, but this is clinically inconsequential according to the manufacturer.
- Take with low fat meal.

INDICATION:

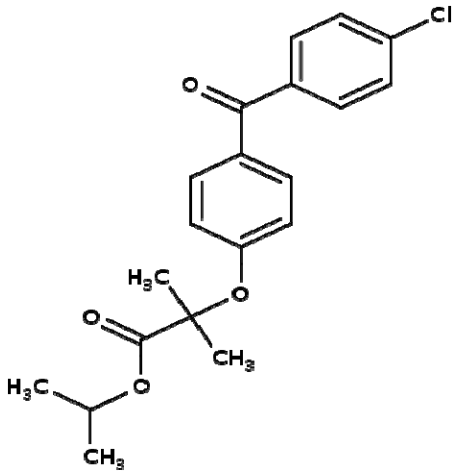
May be used as primary prevention in individuals with multiple risk factors for coronary heart disease (CHD) and as secondary prevention in individuals with CHD to reduce the risk of myocardial infarction (MI), stroke, angina, and revascularization procedures. May be used to reduce the risk of cardiovascular events in patients with acute coronary syndrome (ACS). May be used in the treatment of primary hypercholesterolemia and mixed dyslipidemia, homozygous familial hypercholesterolemia, primary dysbetalipoproteinemia, and/or hypertriglyeridemia as an adjunct to dietary therapy to decrease serum total and low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), and triglyceride concentrations, while increasing high-density lipoprotein cholesterol (HDL-C) levels.

2.FENOFIBRATE

DESCRIPTION:

An antilipemic agent which reduces both cholesterol and triglycerides in the blood.

STRUCTURAL FORMULA:



CHEMICAL NAME:

propan-2-yl 2-{4-[(4-chlorophenyl)carbonyl]phenoxy}-2-methylpropanoate

MOLECULAR FORMULA:

$C_{20}H_{21}ClO$

MOLECULAR WEIGHT:

360.831

EXPERIMENTAL PROPERTIES:

Property	Value
melting point	80.5 °C
Water solubility	0.25mg/ml at 25 °C
logP	5.3

Route of

CLINICAL PHARMACOLOGY:

Mechanism of action

Fenofibrate exerts its therapeutic effects through activation of peroxisome proliferator activated receptor a (PPARa). This increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III. The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles, to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly.

Absorption:

Fenofibrate is well absorbed from the gastrointestinal tract. After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide

Volume of distribution

- 95 L [moderate renal impairment (creatinine clearance of 50 to 90 mL/min)]
- 30 L [healthy adults]

Protein binding:

~99% (Serum protein binding)

Elimination:

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate and 25% was excreted in the feces.

Pharmacodynamics:

Fenofibrate is a lipid regulating agent indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C,Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Fenofibrate is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Fenofibric acid, the active metabolite of Fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteinsapoAI and apoAII.

Half life:

20 hours

Clearance:

1.2 L/h [Eldery]

Toxicity:

LD_{50}=1600 mg/kg (Oral, in mice); Investigated as a teratogen and reproductive hazard.

FOOD INTERACTIONS:

Increased absorption- take with meals.

INDICATION:

For use as adjunctive therapy to diet to reduce elevated LDL-C, Total-C,Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia.[44]

LITERATURE REVIEW

- **Paul M. Lavigne, et al.,** in 2013 had done a study on the Current State of Niacin in Cardiovascular Disease Prevention a Systematic Review and Meta-Regression. This study sought to assess the efficacy of niacin for reducing cardiovascular disease (CVD) events, as indicated by the aggregate body of clinical trial evidence including data from the recently published AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial. Clinical trials of niacin, alone or combined with other lipid-altering therapy, were identified via MEDLINE. Odds ratios (ORs) for CVD endpoints were calculated with a random-effects meta-analyses.Meta-regression modeled the relationship of differences in on-treatment high-density lipoprotein cholesterol with the magnitude of effect of niacin on CVD events.The conclusion shows the consensus perspective derived from available clinical data supports that niacin reduces CVD events and, further, that this may occur through a mechanism not reflected by changes in high-density lipoprotein cholesterol concentration.

- **Robert Krysiak, et al.,** in 2011 studied the effect of *Simvastatin* and *Fenofibrate* on Cytokine Release and Systemic Inflammation in Type 2 Diabetes Mellitus With Mixed Dyslipidemia. compare the effect of simvastatin and fenofibrate treatment on the secretory function of human monocytes and lymphocytes and on systemic inflammation in type 2 diabetes and to assess whether their coadministration is superior to treatment with only 1 of these drugs. The conclusion shows simvastatin and fenofibrate exhibit a similar effect on the secretory function of human monocytes and lymphocytes and on systemic inflammation in type 2 diabetic subjects with mixed dyslipidemia. This effect may be clinically relevant in the prevention of vascular complications in metformin- and diet-treated subjects with newly diagnosed diabetic dyslipidemia.

- **Carl J Fichtenbaum, et al.,** in 2010 performed a Treatment with pravastatin and fenofibrate improves atherogenic lipid profiles but not inflammatory markers in ACTG 5087. Statins and fibrates alter lipids, apolipoproteins, and inflammatory markers in persons without HIV.The conclusion Treatment with pravastatin or fenofibrate improves the atherogenic lipid profile

within the first 12 weeks and is sustained through 48 weeks with combination therapy. Adiponectin levels decrease with lipid-lowering therapy. However, markers of inflammation and platelet activation were not appreciably changed suggesting that the biologic properties of these agents differ in persons with HIV infection.

- **M. John Chapman, et al.,**in 2010 had done a study on atherogenic dyslipidemia using Niacin and fibrates: Pharmacotherapy to reduce cardiovascular risk. statin therapy represents a cornerstone of cardiovascular disease (CVD) prevention, a major residual CVD risk (60–70% of total relative risk) remains, attributable to both modifiable and non-modifiable risk factors. Among the former, low levels of HDL-C together with elevated triglyceride (TG)-rich lipoproteins and their remnants represent major therapeutic targets. The current pandemic of obesity, metabolic syndrome, and type 2 diabetes is intimately associated with an atherogenicdyslipidemic phenotype featuring low HDL-C combined with elevated TG-rich lipoproteins and small dense LDL. Niacin is distinguished by its unique capacity to effectively lower Lp(a) levels. Several studies have demonstrated anti-atherosclerotic action for both niacin and fibrates. In contrast with statin therapy, the clinical benefit of fibrates appears limited to reduction of nonfatal myocardial infarction, whereas niacin (frequently associated with statins and/or other agents) exerts benefit across a wider range of cardiovascular endpoints in studies involving limited patient numbers. Clearly the future treatment of atherogenic dyslipidemias involving the lipid triad, as exemplified by the occurrence of the mixed dyslipidemic phenotype in metabolic syndrome, type 2 diabetes, renal, and auto-immune diseases, requires integrated pharmacotherapy targeted not only to proatherogenic particles, notably VLDL, IDL, LDL, and Lp(a), but also to atheroprotective HDL.

- **Anne C. Goldberg, et al.,** in 2009had done a study on Efficacy and Safety of ABT-335 (Fenofibric Acid) in Combination With Atorvastatin in Patients With Mixed Dyslipidemia. In patients with mixed dyslipidemia characterized by increased triglycerides (TG), decreased high-density lipoprotein (HDL) cholesterol, and increased low-density lipoprotein (LDL) cholesterol, monotherapy with lipid-altering drugs often fails to achieve all lipid targets. Combination therapy was generally well tolerated with a safety profile consistent with those

of ABT-335 and atorvastatin monotherapies. No rhabdomyolysis was reported. The conclusion shows ABT-335 + atorvastatin combination therapy resulted in more effective control of multiple lipid parameters than either monotherapy and may be an appropriate therapy for patients with mixed dyslipidemia.

- **Peter H. Jones, et al.,** in 2009 had done a study on Efficacy and safety of fenofibric acid in combination with a statin in patients with mixed dyslipidemia: Pooled analysis of three phase 3, 12-week randomized, controlled studies**.** In patients with mixed dyslipidemia, combination therapy simultaneously improved multiple lipid abnormalities more effectively than fenofibric acid or statin monotherapies. Combination therapy was generally well tolerated, and safety profiles were similar to monotherapies.

- **Sonja V Sorensen, et al.,** in 2009 had done a study on Model-based simulation to explore the cost-effectiveness of following practice guidelines for triglyceride and low-density lipoprotein cholesterol control among patients with diabetes mellitus and mixed dyslipidemia. The National Cholesterol Education Program Adult Treatment Panel III guidelines recommend maintaining lipid levels within particular targets to reduce the risk of coronary heart disease (CHD) events. A simulation model using a US health care payer perspective was designed to predict changes in lipid levels (LDL-C, TG, high-density lipoprotein cholesterol, and total cholesterol) and long-term CHD risk. The results of this model simulation suggest that for patients with DM and mixed dyslipi-demia, following treatment guidelines rather than current practice (including combination therapy rather than monotherapy) would result in more patients achieving lipid targets, fewer CHD events, and more QALYs gained at a reasonable cost (less than $109,000) per QALY.

- **Sergio Fazio, et al.,** in 2008 had done a study on management of mixed dyslipidemia in patients with or at risk for cardiovascular disease. Lowering low-density lipoprotein cholesterol (LDL-C) is the primary focus of the management of dyslipidemia in patients with or at risk for cardiovascular disease. The addition of fenofibrate to statin therapy may be a useful strategy for the management of mixed dyslipidemia in patients with or at risk for cardiovascular disease.

- **Gloria Lena Vega, et al.,** in 2006 had done a study on Combination of fenofibrate plus low-dose nicotinic acid added to statin treatment in type 2 diabetes. Plasma lipid abnormalities commonly persist in patients with diabetic dyslipidemia in spite of statin monotherapy. Fenofibrate plus low-dose nicotinic acid adequately improves the lipoprotein profile in patients with diabetic dyslipidemia who are being treated with a statin. Plasma levels of total cholesterol, triglycerides, very-low-density lipoprotein plus intermediate-density lipoprotein cholesterol (VLDL+IDL-C), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B were also measured. The conclusion shows that reatment with the 3-drug regimen was associated with a significant reduction in triglyceride levels compared with simvastatin monotherapy. However, there was not a significant incremental reduction in triglyceride levels when nicotinic acid was added to the 2-drug treatment, suggesting that the triglyceride-lowering effect of fenofibrate + nicotinic acid is not cumulative. To obtain clinically meaningful responses, particularly for the treatment of elevated HDL-C, higher doses of nicotinic acid might be required.

- **FD Richard Hobbs, et al.,** in 2006 explained about the Reduction of cardiovascular risk in diabetes: Beyond glycemic and blood pressure control. Patients with diabetes mellitus have a much higher rate of cardiovascular disease (CVD) than the general population, and, in addition to glycaemia and hypertension, dyslipidemia has emerged as an important modifiable cardiovascular risk factor in these patients. In most patients with type 2 diabetes, the major features of dyslipidemia are increased triglyceride levels, decreased high-density lipoprotein cholesterol (HDL-C) levels, and changes in the composition and level of low-density lipoprotein cholesterol (LDL-C). Clinical trials evaluating both primary and secondary prevention of CVD demonstrate that lipid-lowering therapy results in a substantial reduction of cardiovascular risk in patients with type 2 diabetes. Low-density lipoprotein cholesterol is the first priority for treatment, with a statin in adequate dosage as the first choice for pharmacological therapy. The first statin trial conducted solely in patients with type 2 diabetes and no prior CVD demonstrated a 37% reduction in cardiovascular events in patients randomized to atorvastatin 10 mg compared with placebo. Additional trials that further address the benefits of lipid-lowering therapy in patients with diabetes are near

completion, or are underway, and should provide important information about further attenuating risk in patients with diabetes.

- **Michael H. Davidson, et al.,** in 2005 had done a study on Efficacy and safety profile of fenofibrate-coated microgranules 130 mg, with and without food, in patients with hypertriglyceridemia and the metabolic syndrome. The limited bioavailability of certain fenofibrate formulations necessitates administration with food, raising concerns about efficacy and compliance. There is a need for new formulations that have improved bioavailability and eliminate the requirement for administration with food.The conclusion shows that this study found no inequivalence in the TG-lowering effects of the 2 fenofibrate regimens compared with placebo. Both regimens were well tolerated. Thus, FF-μG 130 mg administered without regard to meals appears to be efficacious and well tolerated for the treatment of hypertriglyceridemia in patients exhibiting the metabolic syndrome.

- **Robert S Rosenson, et al.,** in 2005 studied the new approaches in the intensive management of cardiovascular risk in the metabolic syndrome .The risk factors such as dyslipidemia and hypertension are inadequately controlled in subjects with the metabolic syndrome by lifestyle interventions, pharmacologic approaches are warranted. Statins are first-line pharmacotherapy for dyslipidemia due to their efficacy for lowering low-density lipoprotein (LDL) cholesterol and may also improve high-density lipoprotein (HDL) cholesterol and triglyceride levels. Fibrates and niacin may be useful in combination with a statin for additionally lowering triglycerides or raising HDL cholesterol. Adequate control of hypertension will usually require two or more drugs; agents that block the renin-angiotensin system are particularly useful in this population, given their demonstrated benefits for reducing the burden of cardiovascular events and end-stage renal disease independent of blood-pressure lowering. A multifaceted approach to risk factor management for the metabolic syndrome will have benefits for prevention of type 2 diabetes and cardiovascular disease.

- **Verny C, et al.,** in 2005 explained the management of dyslipidemia in elderly diabetic patients. The prevalence of diabetes increases with age, potentially affecting 20% of the 75

years and older elderly population. Overmortality and increased cardiovascular morbidity-mortality are common in diabetic populations, including elderly diabetes. This increased cardiovascular risk must therefore be taken into consideration when discussing management of dyslipidemia in elderly diabetics. Should dyslipidemia be treated in elderly diabetics? What are the objectives and with what means? Whether the significance of dyslipidemia is different in this growing population compared with younger subjects remains unknown due to the lack of specific studies. The only results available come from a few primary or secondary cardiovascular prevention trials using statins or fibrates with subgroups of elderly diabetic patients, or subgroups of diabetic patients and also subgroups of patients aged over 65. Three recent studies detailed the potential benefit of such treatment: PROSPER in elderly subjects aged 70-82 years, HPS in diabetics before and after the age of 70 years and CARDS in diabetics aged up to 75 years. The results of these studies provide a few indirect elements of interest, keeping in mind the generally higher iatrogenic risk of treatment in elderly populations.

- **Giuseppe Derosa,et al.,** in 2004 had done a study on Comparison of fluvastatin + fenofibrate combination therapyandfluvastatinmonotherapy in the treatment of combined hyperlipidemia,type 2 diabetes mellitus, and coronary heart disease: a 12-month, randomized, double-blind, controlled trial. Diabetes risk is often complicated by a mixed hyperlipoproteinemia not sufficiently controlled by a single antihyperlipidemic drug; however, there are some concerns about the safety of combined statin and fibrate treatments. The conclusion shows that the patients with combined hyperlipidemia, type 2 DM, and CHD, the combination of extended-release fluvastatin + micronized fenofibrate was associated with a more improved lipid profile than fluvastatinmonotherapy, and was a well-tolerated and cost-effective therapeutic choice to treat these patients at high risk for CVD.

- **Antonios M Xydakis, et al.,** in 2002 had done a study on Combination therapy for combined dyslipidemia.Patients with combined dyslipidemia are at high risk for coronary artery disease and often require combination drug therapy to achieve lipid levels recommended by the US National Cholesterol Education Program's third Adult Treatment Panel (ATP III). In addition to recommendations for low-density lipoprotein (LDL) cholesterol and triglyceride levels,

ATP III established non–high-density lipoprotein (HDL) cholesterol goals for individuals with triglycerides ≥2.26 mmol/L (≥200 mg/dL). It also introduced certain criteria for the diagnosis of the metabolic syndrome, a clustering of risk factors (abdominal obesity, elevated triglycerides, low HDL cholesterol, elevated blood pressure, impaired fasting glucose) that increases cardiovascular risk and is common in patients with combined dyslipidemia. Statin monotherapy has been shown to benefit these patients, and additional benefit may be obtained by combination therapy that provides greater reductions in both LDL cholesterol and triglycerides as well as greater increases in HDL cholesterol. Recently developed agents that may improve the effectiveness of combination therapy include ezetimibe—a cholesterol absorption inhibitor—and a formulation that combines extended-release niacin and lovastatin in a single pill. Clinical trials are needed to determine the optimal treatment in patients with combined dyslipidemia.

- **Michael H Davidson, et al.,** in 2002 had done a study on Combination therapy for dyslipidemia: safety and regulatory considerations. The use of combination therapy is an effective way to manage dyslipidemia in patients with coronary artery disease (CAD). Aggressive lipid-altering therapy often requires the use of combination therapy involving statins in conjunction with niacin, fibric-acid derivatives, ezetimibe, or bile acid resins. Yet, safety concerns regarding the combination of statins with other lipid-altering drugs and patient acceptance of combination therapy have influenced its application in the treatment of CAD.

- **Peter H Jones, et al.,** had done a study on Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia. The conclusion shows that patients with mixed dyslipidemia, combination therapy with ABT-335 + rosuvastatin resulted in more effective control of multiple lipid parameters than either monotherapy alone, with a safety profile similar to both monotherapies.

- **Jadwiga Najib, et al.,** had done a study onFenofibrate in the treatment of dyslipidemia: A review of the data as they relate to the new suprabioavailable tablet formulation. The fibric acid derivative fenofibrate is indicated as an adjunct to dietary modification in adults with

primary hypercholesterolemia or mixed dyslipidemia (types IIa and IIb hyperlipidemia, Fredrickson classification) to reduce levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and apolipoprotein (apo) B, and to increase levels of high-density lipoprotein cholesterol (HDL-C) and apo A. Fenofibrate is effective in reducing levels of TG, TC, and LDL-C, and increasing levels of HDL-C in patients with dyslipidemias. Its efficacy and tolerability in the treatment of hypertriglyceridemia and combined hyperlipidemia have been demonstrated in numerous clinical trials. Its use is accompanied by a low incidence of adverse effects and laboratory abnormalities. Fenofibrate protects against coronary heart disease not only through its effects on lipid parameters but also by producing alterations in LDL structure and, possibly, alterations in the various hemostatic parameters. Its uricosuric property may prove to be a useful adjunctive attribute

AIM AND OBJECTIVES

AIM

The aim of the study is to evaluate and compare the efficacy and safety of Atorvastatin alone and in combination with Fenofibrate in Dyslipidemic patients at Dharmapuri, Tamilnadu**.**

OBJECTIVE

- To evaluate and compare the efficacy of atorvastatin as monotherapy alone and as combination therapy with fenofibrate.
- To evaluate and compare the safety of atorvastatin alone and in combination with fenofibrate.
- To compare the efficacy of both therapies among male and female dyslipidemic patients.
- To compare the efficacy of both therapies on diabetic and non-diabetic dyslipidemic patients.

PLAN OF THE WORK

The entire study was planned to be carried out for a period of a ten months from December 2012 to August 2013.

The proposal was designed as given below.

PROPOSAL

December – January 2013

- Literature survey.
- Obtaining Consent from the hospital authority.
- Study design including design of data entry form**.**

Feb – June 2013

- Selection of Patients.
- Obtaining consent from the patients.
- Collection of Patient Details.
- Collection of Lab data.

June – August 2013

- Compilation
- Data analysis
- Submission of reports

METHODOLOGY

- **Site of Study** :

  Suba Medical Centre And Hospital, Dharmapuri.

- **Department Selected for Study** :

  Cardiology department

- **Institutional ethics committee approval**
- **Consent From Hospital Authority**
- **Study Design**

Institutional ethics committee

A protocol of the study, which includes the objectives, methodology, etc, was submitted to "**Institutional ethics committee"** for approval of the study.

STUDY DESIGN

- Patient selection
- Patient groups
- Design of proforma

Patient Selection

Patient Inclusion Criteria:

Patients on dyslipidaemic drugs

Both genders

Age between 18 to 80 years

Patients co-morbid conditions such as

Diabetes Mellitus

Coronary Artery Disease

Myocardial Infarction

Hypertension

Patient Exclusion Criteria

Pregnant or lactating women

Patients with any co-morbidity such as

Acute emergency hypertensive patients

Renal transplant patients

Liverdiseased patients

Malignant patients

Hereditary or acquired myopathy

Hypersensitivity to study medications

PatientGroups

- Patients grouped into two:

Group-A Group-B

Patients having either high level of LDL-C or TG or both than that of normal level were put under the Group A and patients having abnormal level of LDL-C, TG and HDL-C were put under the Group B.

Group-A: Receiving atorvastatin only (Monotherapy).

Group-B: Receiving both atorvastatin and fenofibrate (Combination therapy).

No of Patients:

Total no of patients: 80

Group-A : 40 patients

Group-B : 40 patients

WORK METHODOLOGY

- On basis of inclusion and exclusion criteria, totally 80 patients were selected and their base line lipid profile values, heart rates, blood pressure fasting blood glucose, plasma urea and creatinine and drugs used for the treatment were noted.
- Then the data of the same patients after drug therapy after that is after 6 months were taken as the review value. Side effects reported by patients were noted.

The values obtained under the base and review in both the groups were analyzed using the suitable statistical methods such as

- **column statistics**
- **paired t- test**

Using the software "graph pad -prism 5 for windows version 5.01"

DESIGNOFPROFORMA

PROFORMA I : PATIENT INFORMED CONSENT FORM

PROFORMA II : PATIENT DETAILS FORM

PROFORMA III : LAB INVESTIGATION CHART

PROFORMA IV : MEDICATION CHART

PROFORMA V : ADVERSE DRUG REACTION FORM

RESULTS

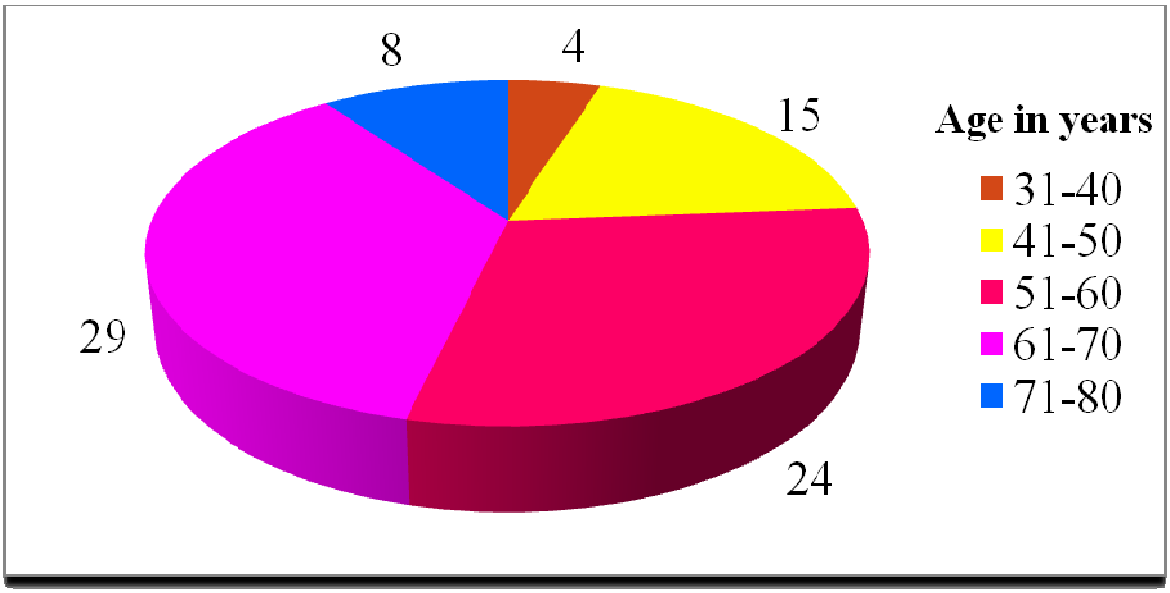
AGE WISE DISTRIBUTION OF THE STUDY PATIENTS

S.No	Age in years	No. of patients	Percent(%)
1.	31-40	4	5
2.	41-50	15	18.75
3.	51-60	24	30
4.	61-70	29	36.25
5.	71-80	8	10
	Total no. of patients	**80**	**100**

TABLE:1

AGE WISE DISTRIBUTION OF THE STUDY PATIENTS (n=80)

PERCENTAGE



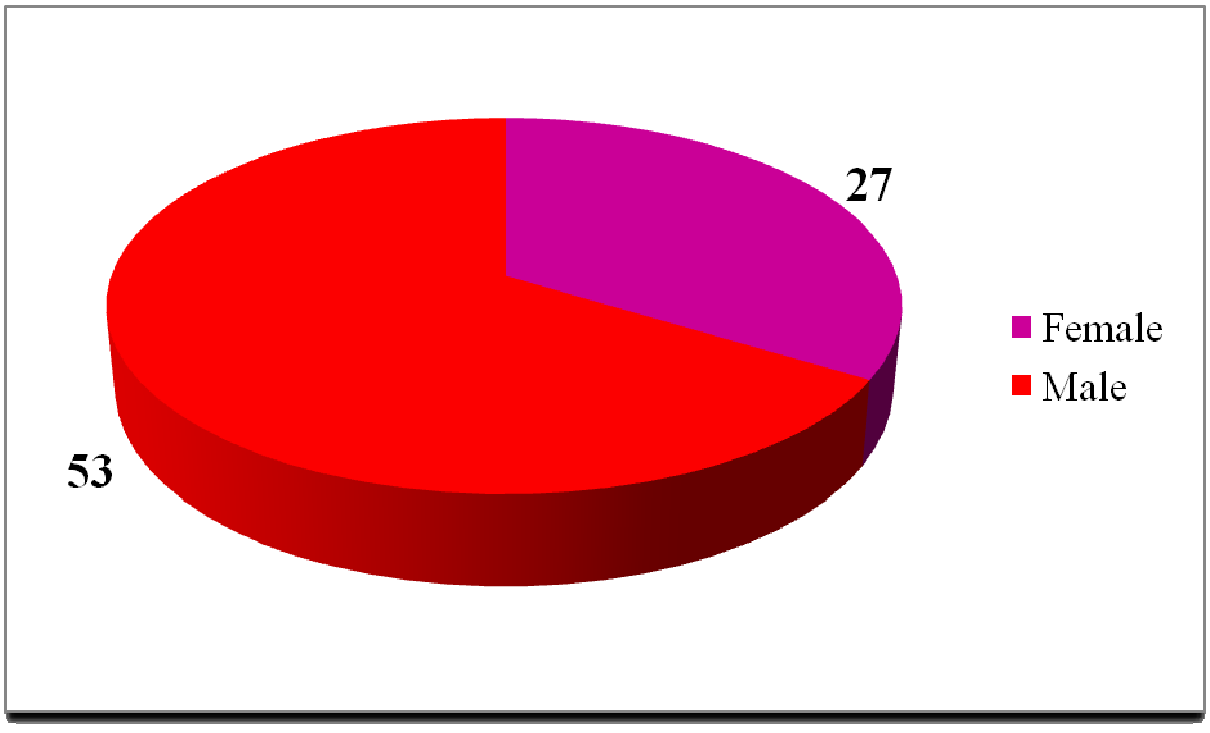
GENDER WISE DISTRIBUTION OF THE SELECTED PATIENTS

S.No	Gender	No. of patients	Percent(%)
1.	Female	27	33.75
2.	Male	53	66.25
	Totalno.of patients	80	100

TABLE:2

GENDER WISE DISTRIBUTION OF THE SELECTED PATIENTS (n=80)

PERCENTAGE



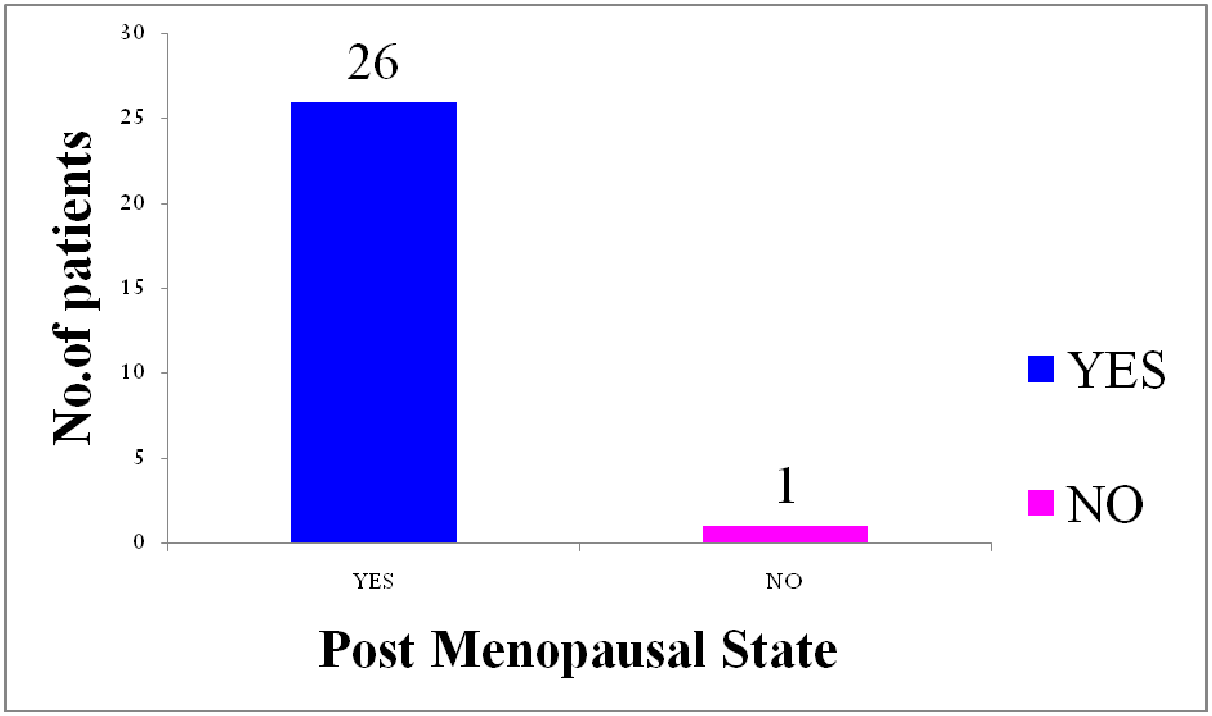
POST MENOPAUSAL STATE OF THE INCLUDED FEMALE PATIENTS

S.No	Post menopausal state	No.of patients	Percent(%)
1.	Yes	26	96.29
2.	No	1	0.37
	Total no. of female patients	27	100

TABLE:3

POST MENOPAUSAL STATE OF THE INCLUDED FEMALE PATIENTS (n=27)

PERCENTAGE



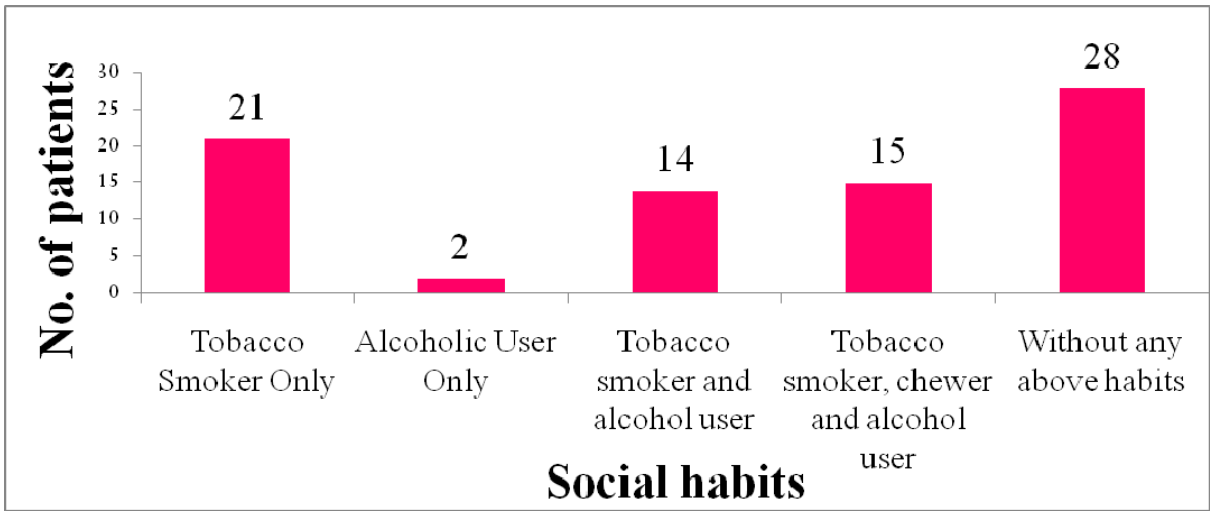
SOCIAL HABITS OF THE INCLUDED PATIENTS (n=80)

S.No	Social habits	No. of Patients	Percent(%)
1.	Tobacco Smoker Only	21	26.25
2.	Alcohol User Only	02	02.50
3.	Tobacco Smoker and Alcohol User	14	17.50
4.	Tobacco Smoker, Chewer and Alcohol User	15	18.75
5.	Without Any Above Habits	28	35.00
	Total No. of Patients	**80**	**100**

TABLE:4

SOCIAL HABITS OF THE INCLUDED PATIENTS (n=80)

PERCENTAGE



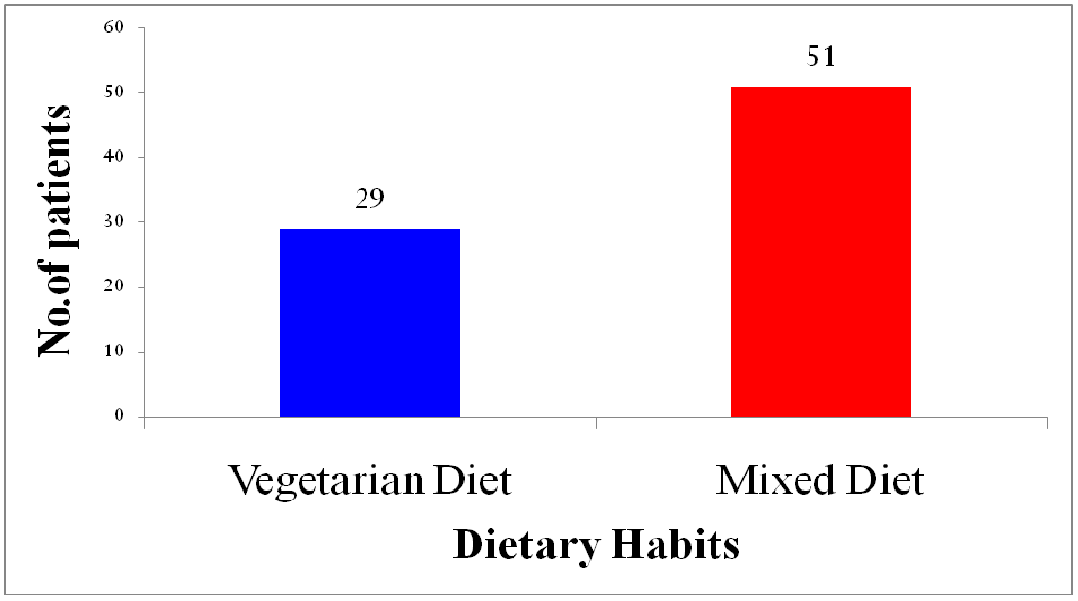
DIETARY HABITS OF THE STUDY PATIENTS

S.No	Diet	No.of patients	Percent(%)
1.	Vegetarian Diet	29	36.25
2.	Mixed Diet	51	63.75
	Total no. of patients	**80**	**100**

TABLE:5

DIETARY HABITS OF THE STUDY PATIENTS (n=80)

PERCENTAGE



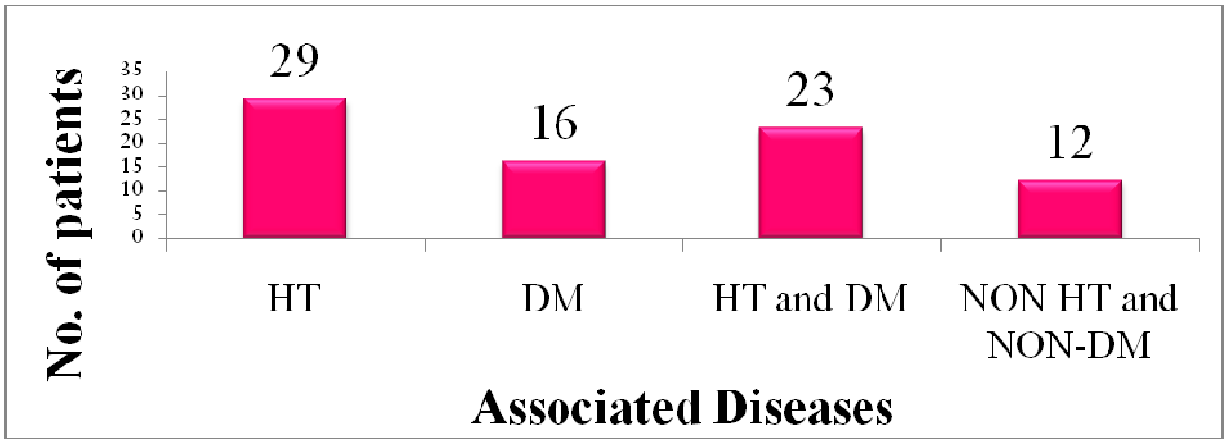
ASSOCIATED DISEASES OF THE STUDY PATIENTS

S.No	Associated diseases	No. of patients	Percent(%)
1.	HT	29	36.25
2.	DM	16	20.00
3.	HT and DM	23	28.75
4.	NON-HT and NON-DM	12	15.00
	Total no. of patients	**80**	**100**

TABLE:6

ASSOCIATED DISEASES OF THE STUDY PATIENTS

PERCENTAGE



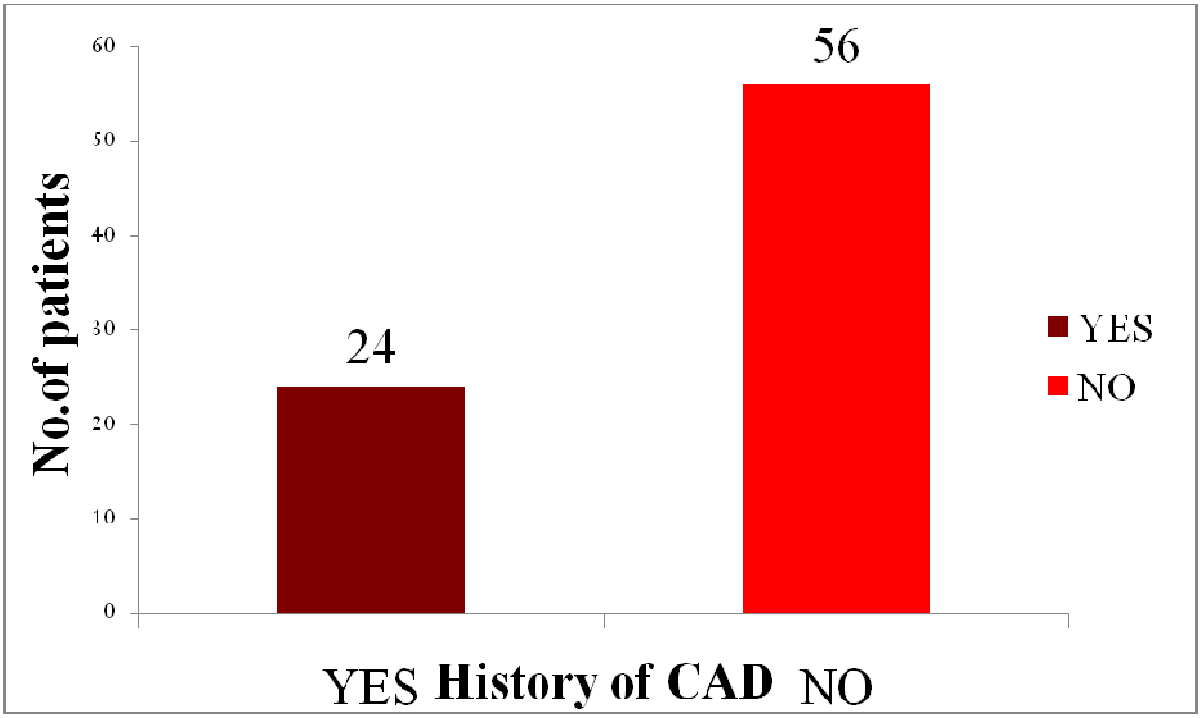
HISTORIES OF CORONARY ARTERY DISEASES OF THE STUDY PATIENTS

S.No	History of CAD	No. of patients	Percent(%)
1.	Yes	24	30
2.	No	56	70
	Total no. of patients	80	100

TABLE:7

HISTORIES OF CORONARY ARTERY DISEASES OF THE STUDY PATIENTS

PERCENTAGE



Effect of Atorvastatin Alone and in Combination with Fenofibrate on Lipid Parameter of Dyslipidemic Patients

Lipid parameters	Monotherapy (n=40)			Combination therapy (n=40)		
	Base (mg/dL)	**Review** (mg/dL)	**Mean % Change (%)**	**Base** (mg/dL)	**Review** (mg/dL)	**Mean % Change (%)**
TC	180.4 ± 29.81	151.1 ± 19.77***	-16.24	176.2 ± 44.86	148.1 ± 23.07***	-15.95
TG	168.4 ± 33.16	140.5 ± 33.37**	-16.57	233.1 ± 59.66	153.8 ± 55.96***	-34.02
HDL-C	39.63 ± 6.28	39.88 ± 5.94	+0.63	33.67 ± **7**.83	42.25 ± 13.83***	+25.48
LDL-C	110.3 ± 26.64	83.49 ± 11.58***	-24.4	105.2 ± 41.19	77.73 ± 17.75***	-26.11
VLDL-C	34.96 ± 8.47	28.68 ± 6.91***	-17.96	46.27 ± 11.79	30.77 ± 11.21***	-33.50

Data presented are Mean ± SD

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

TABLE:8

Effect of Atorvastatin Alone on
Lipid Parameter of Dyslipidemic Patients

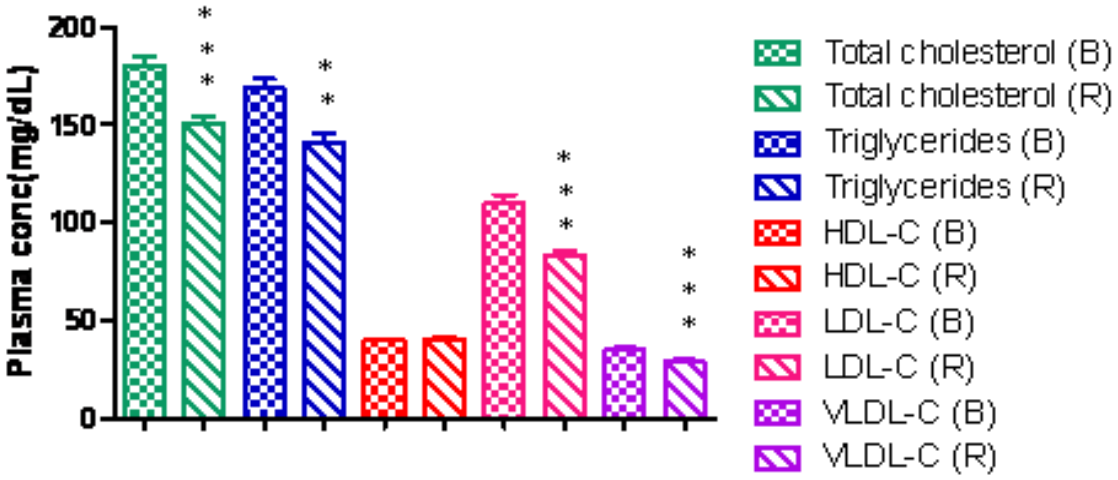


Figure presented are Mean ± SE

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

B – Base, R- Review

Effect of Atorvastatin in Combination with Fenofibrate on Lipid Parameter of Dyslipidemic Patients

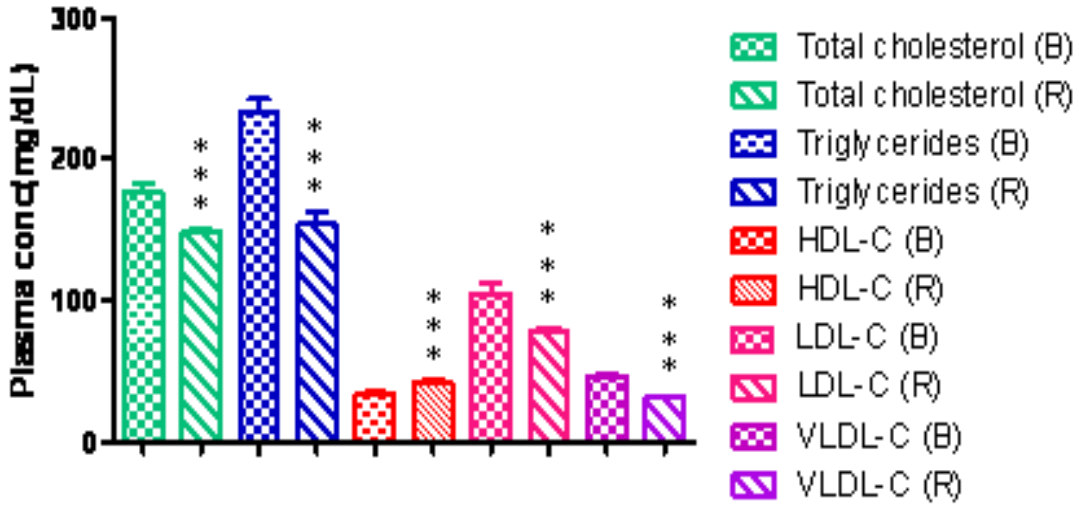
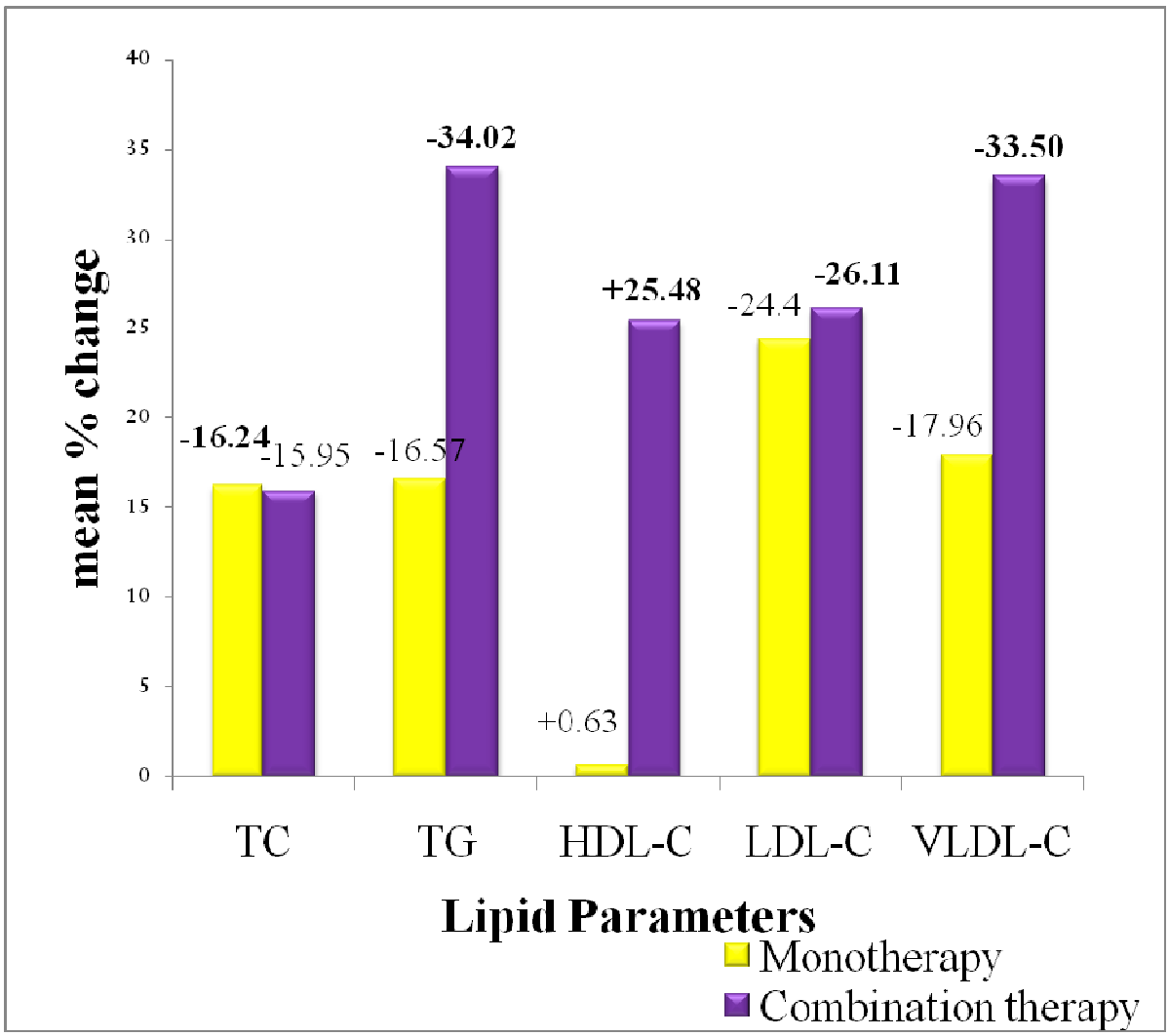


Figure presented are Mean ± SE

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't"test

B – Base, R- Review

Mean Percentage Change of Lipid Parameters After Atorvastatin Alone (n=40) and Combination With Fenofibrate (n=40)



Effect of Atorvastatin Alone and in Combination with Fenofibrate on Heart Rate of Dyslipidemic Patients

S.No	Drug Therapy	Base Value (beats/min)	Review Value (beats/min)	Percent Change (%)
1.	Monotherapy	74.85 ± 2.94	74.05 ± 2.55	-1.07
2.	Combination Therapy	75.55 ± 2.55	74.03 ± 2.86	-2.01

Data presented are Mean ± SD

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

TABLE:9

Effect of Atorvastatin Alone and in Combination with Fenofibrate on Heart Rate of Dyslipidemic Patients

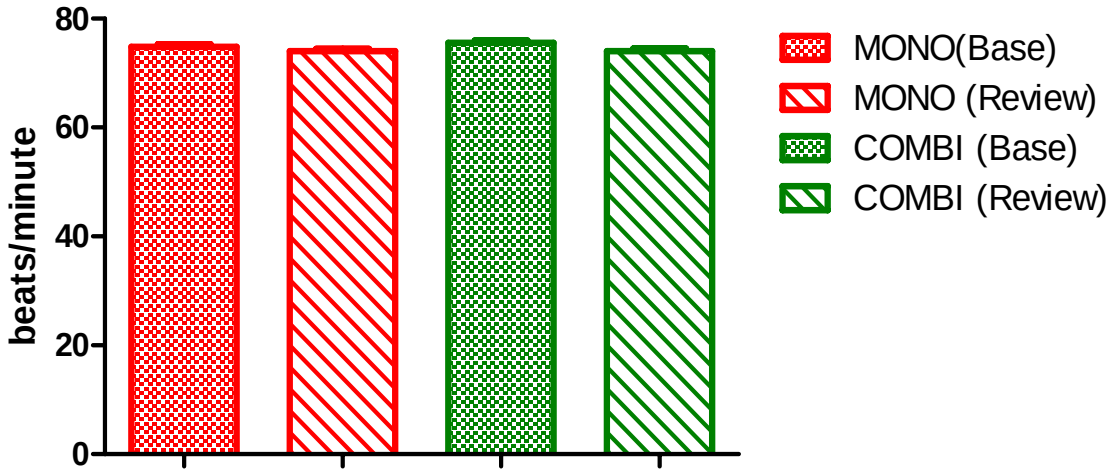


Figure presented are Mean ± SE

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't"test

Effect of Atorvastatin Alone and in Combination with Fenofibrate on BPof Dyslipidemic Patients

Drug Therapy	**Systolic**			**Diastolic**		
Monotherapy (n= 40)	Base Value	Review Value	Percent Change **(%)**	Base Value	Review Value	Percent Change **(%)**
	141.6 ± 15.12	128.1 ± 5.87***	-9.53	84.0 ± 7.18	76.23 ± 5. 87***	-9.25
Combination Therapy (n= 40)	143.1 ± 11.91	128.5 ± 9.85***	-10.20	88.2 ± 7.52	76.6 ± 5.73**	-13.15

Data presented are Mean ± SD

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

TABLE:10

Effect of Atorvastatin Alone and in Combination with Fenofibrate on BPofDyslipidemic Patients

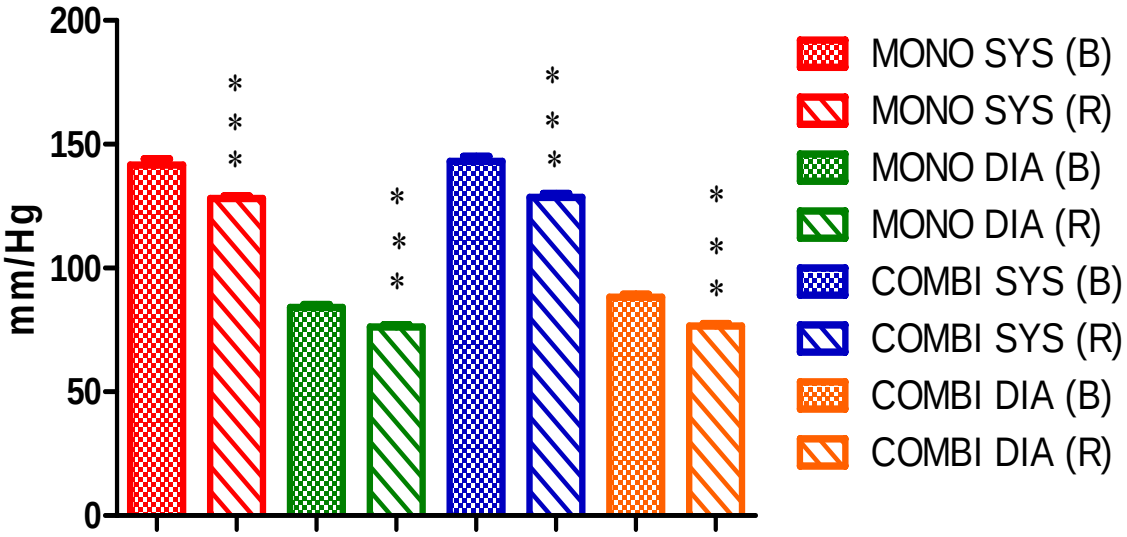


Figure presented are Mean ± SE

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't"test

Effect of Atorvastatin Alone and in Combination with Fenofibrate on Fasting Blood Glucose of Dyslipidemic Patients

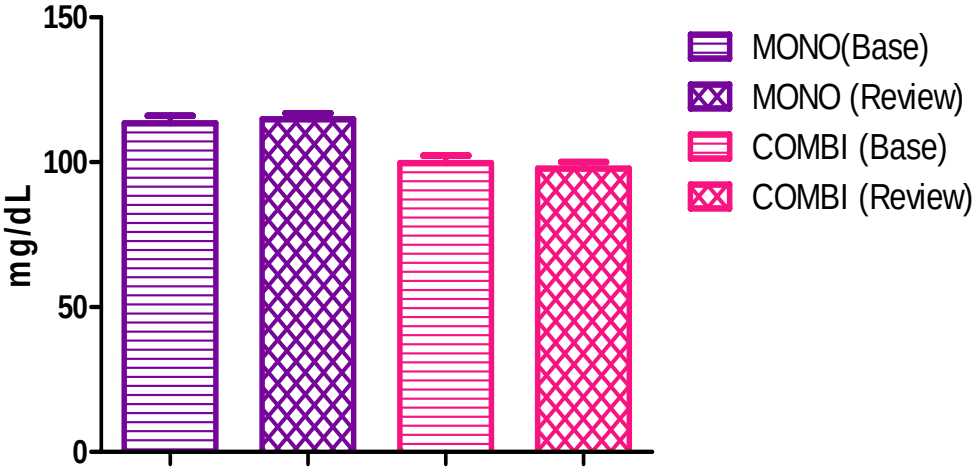
S.No	Drug Therapy	Base Value (beats/min)	Review Value (beats/min)	Percent Change(%)
1.	Monotherapy	113.5 ± 16.32	114.8 ± 13.3	+1.14
2.	Combination Therapy	99.69 ± 16.97	97.84 ± 13.7	-1.85

Data presented are Mean ± SD

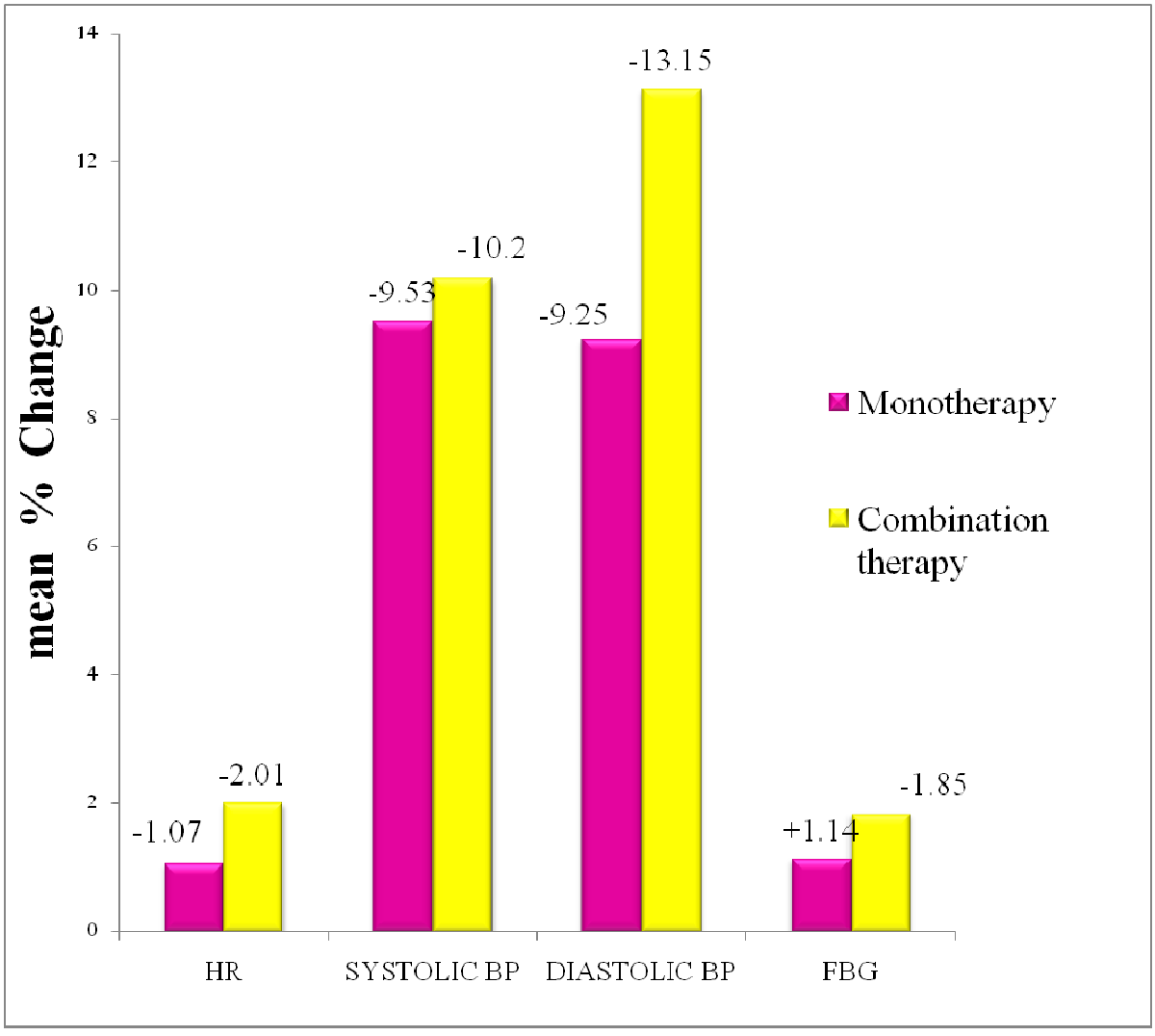
p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

TABLE:11

Effect of Atorvastatin Alone and in Combination with Fenofibrate on Fasting Blood Glucose of Dyslipidemic Patients



Mean Percentage Change of Heart Rate, Systolic BP, Diastolic BP and Fasting Blood Glucose After Atorvastatin Alone (n=40) and Combination with Fenofibrate (n=40)



Effect of Atorvastatin Alone (n=40) and in Combination with Fenofibrate on Renal Functions of Dyslipidemic Patients (n=40) After Drug Therapy

S.No	Parameters	Monotherapy (mg/dl)	Combination Therapy (mg/dl)	Normal level (mg/dl)
1.	Urea	25.13	28.34	10-40
2.	Creatinine	1.18	1.20	0.7-1.4

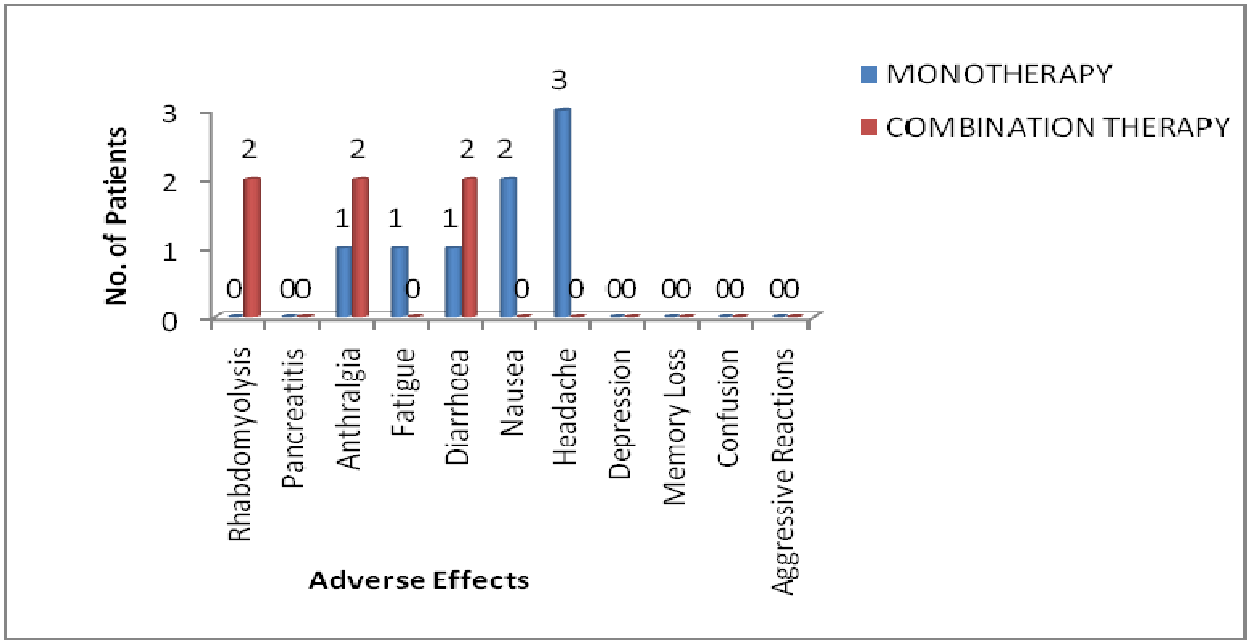
TABLE:12

Adverse Drug Reaction of Atorvastatin Alone (n=40) and in Combination with Fenofibrate of Dyslipidemic Patients (n=40)

Adverse Reactions	Monotherapy	Combination Therapy
Rhabdomyolysis	0	2
Pancreatitis	0	0
Anthralgia	1	2
Fatigue	1	0
Diarrhoea	1	2
Nausea	2	0
Headache	3	0
Depression	0	0
Memory Loss	0	0
Confusion	0	0
Aggressive Reactions	0	0

TABLE:13

Adverse Drug Reaction of Atorvastatin Alone (n=40) and in Combination with Fenofibrate of Dyslipidemic Patients (n=40)



Effect of Atorvastatin alone on Male and Female Dyslipidemic Patients Separately (n=40)

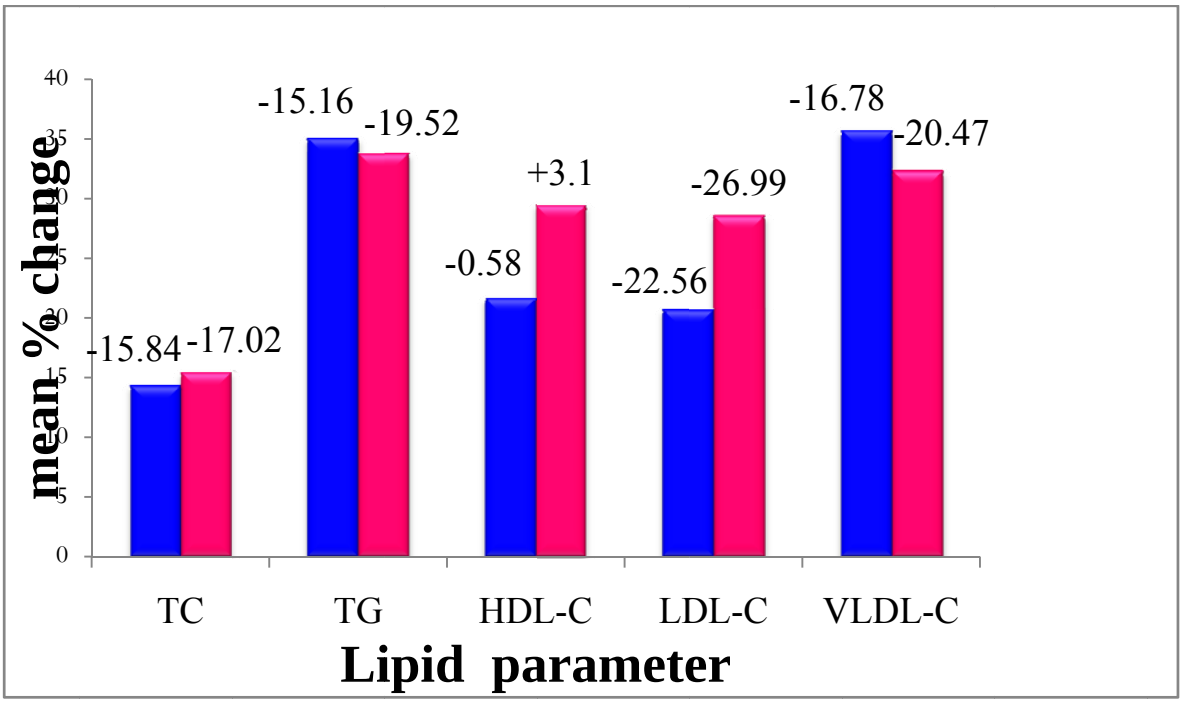
Lipid Parameters	Male (n=27)			Female (n=13)		
	Base (mg/dL)	Review (mg/dL)	Mean % Change	Base (mg/dL)	Review (mg/dL)	Mean% Change
TC	178.7 ± 32.66	150.4 ± 21.98 ***	-15.84	183.9 ± 23.56	152.6 ± 14.81***	-17.02
TG	170.8 ± 35.21	144.9 ± 37.53**	-15.16	163.4 ± 29.12	131.5 ± 20.93*	-19.52
HDL-C	39.43 ± 5.01	39.2 ± 5.99	-0.58	40.05 ± 8.57	41.29 ± 5.8	+3.10
LDL-C	107.7 ± 27.39	83.4 ± 11.5***	-22.56	114.6 ± 25.41	83.67 ± 12.22 ***	-26.99
VLDL-C	35.33 ± 9.86	29.4 ± 7.88 **	-16.78	34.2 ± 4.69	27.2 ± 4.11***	-20.46

Data presented are Mean ± SD

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

TABLE:14

Mean Percentage Change of Lipid Parameters on Treatment with Atorvastatin Alone on Male (n=27) and Female (n=13) Dyslipidemic Patients Separately



Effect of Atorvastatin in Combination with Fenofibrate on Male and Female Dyslipidemic Patients Separately (n=40)

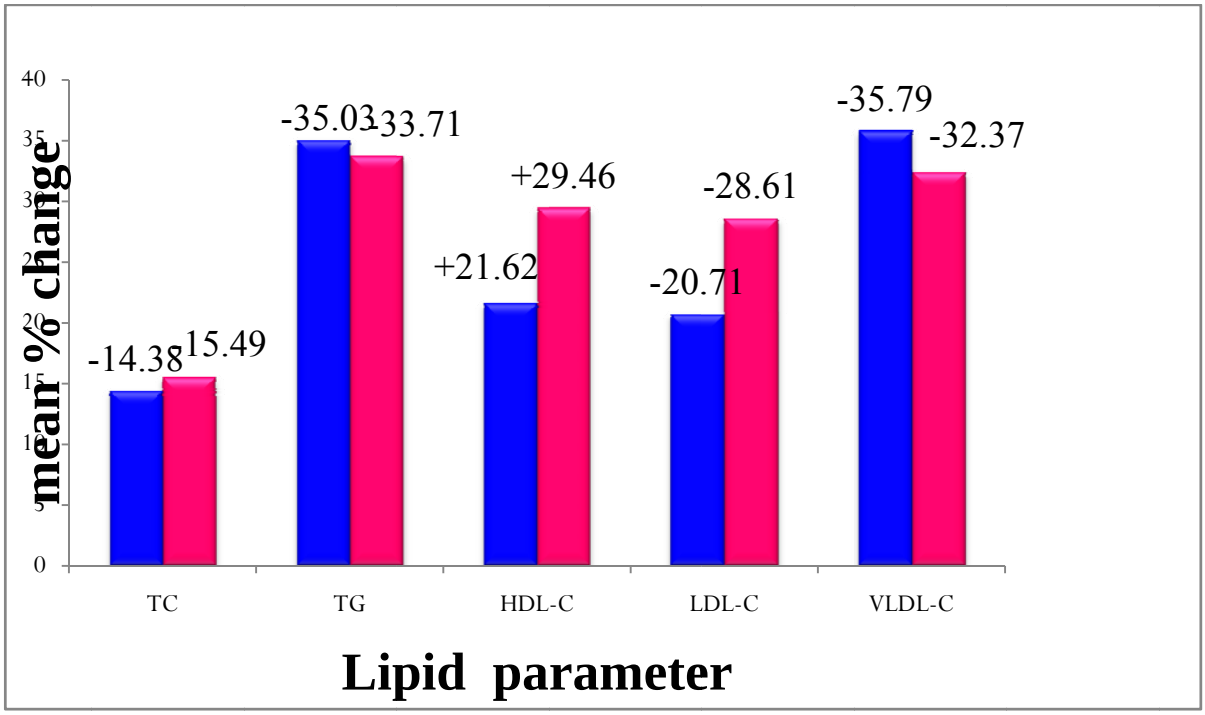
Lipid Parameters	Male (n=26)			Female (n=14)		
	Base (mg/dL)	Review (mg/dL)	Mean% Change	Base (mg/dL)	Review (mg/dL)	Mean% Change
TC	175.3 ± 36.56	149.5 ± 25.08**	-14.72	178 ± 58.84	145.5 ± 19.38*	-18.26
TG	232.3 ± 65.27	163.2 ± 64.09***	-29.75	234.7 ± 49.82	136.3 ± 31.48 ***	-41.92
HDL-C	31.25 ± 5.8	40.2 ± 9.67 ***	+28.64	38.15 ± 9.27	46.05 ± 19.24*	+20.70
LDL-C	106 ± 34.33	80.54 ± 18.55 ***	-24.02	103.6 ± 53.11	72.53 ± 15.45 *	-29.99
VLDL-C	46.63 ± 12.9	33.04 ± 12.68***	-29.14	45.6 ± 9.81	26.55 ± 6.21***	-41.78

Data presented are Mean ± SD

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

TABLE:15

Mean Percentage Change of Lipid Parameters on Treatment with Atorvastatin in Combination With Fenofibrate on Male (n=26) and Female (n=14)Dyslipidemic Patients Separately



Effect of Atorvastatin Alone on Diabetic and Non-Diabetic Patients (n=40)

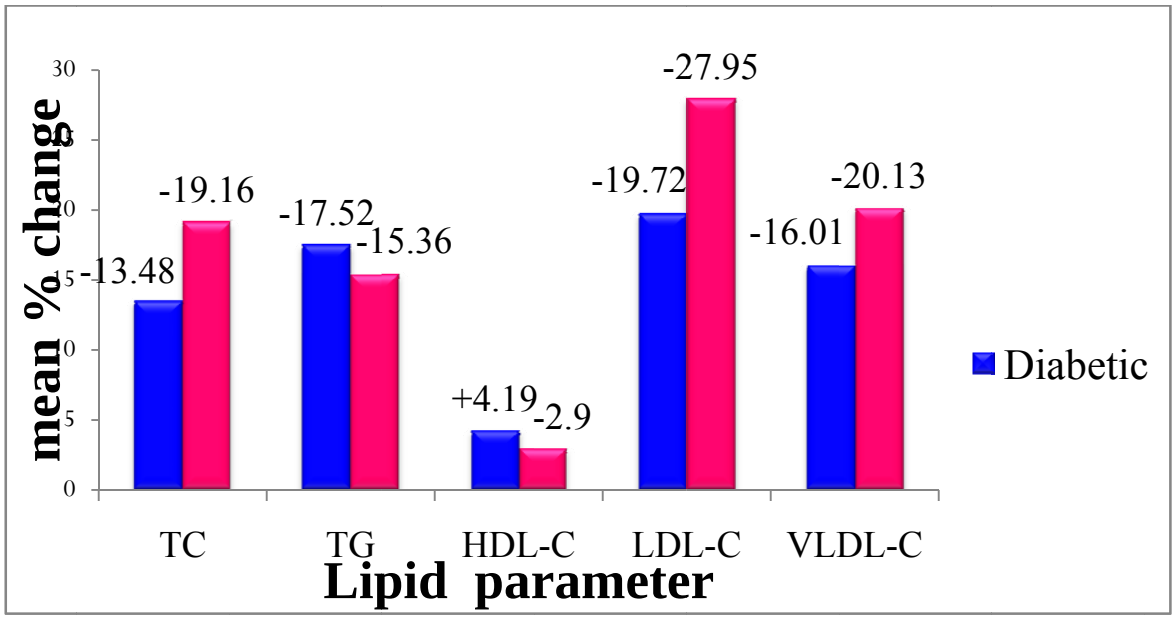
Lipid Parameters	Diabetic Patients (n=19)			Non-Diabetic Patients (n=21)		
	Base (mg/dL)	Review (mg/dL)	Mean% Change	Base (mg/dL)	Review (mg/dL)	Mean% Change
TC	175.1 ± 30.53	151.5 ± 19.06***	-13.48	186.3 ± 28.62	150.6 ± 21.03 ***	-19.16
TG	175.8 ± 23.6	145 ± 38 **	-17.52	160.1 ± 40.33	135.5 ± 27.56*	-15.36
HDL-C	37.74 ± 4.68	39.32 ± 6.78	+4.19	41.72 ± 7.23	40.51 ± 4.96	-2.9
LDL-C	103.17 ± 30.04	82.82 ± 10.57 **	-19.72	116.9 ± 20.91	84.22 ± 112.86 ***	-27.95
VLDL-C	35.17 ± 4.84	29.54 ± 8.05**	-16.01	34.73 ± 11.38	27.74 ± 5.44 **	-20.13

Data presented are Mean ± SD

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

TABLE:16

Mean Percentage Change of Lipid Parameters after Treatment with Atorvastatin alone on Diabetic (n=19) and Non-Diabetic (n=21) Patients



Effect of Atorvastatin in Combination with Fenofibrate on Diabetic and Non-Diabetic Patients (n=40)

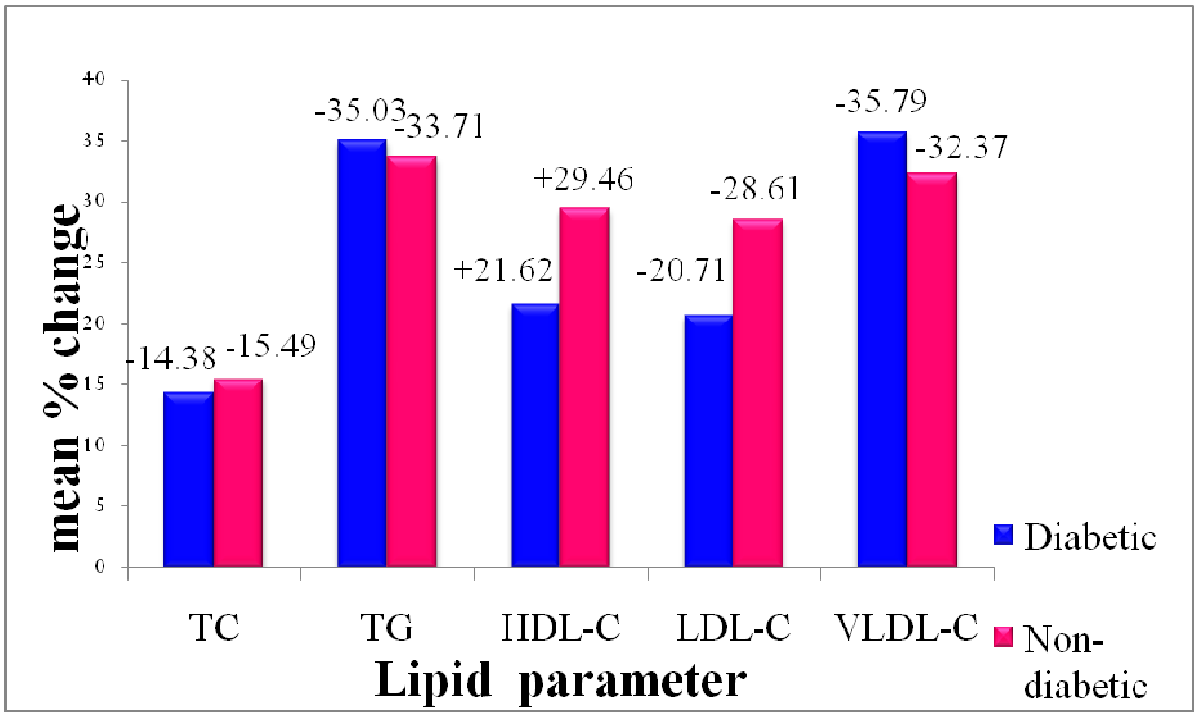
Lipid Parameters	Diabetic Patients (n=27)			Non-Diabetic Patients(n=13)		
	Base (mg/dL)	Review (mg/dL)	Mean% Change	Base (mg/dL)	Review (mg/dL)	Mean% Change
TC	171.7 ± 36.99	147 ± 17.94 **	-14.38	174.9 ± 53.07	147.8 ± 27.08 *	-15.49
TG	243.2 ± 73.29	158 ± 64.76 ***	-35.03	222.2 ± 37.14	147.3 ± 43.62 ***	-33.71
HDL-C	33.03 ± 5.16	40.17 ± 7.28 ***	+21.62	33.54 ± 9.88	43.42 ± 18.05 **	+29.46
LDL-C	102.7 ± 35.06	81.43 ± 16.32 **	-20.71	103.1 ± 46.88	73.6 ± 18.08 **	-28.61
VLDL-C	48.62 ± 14.64	31.22 ± 13.08***	-35.79	43.53 ± 6.98	29.44 ± 8.7 ***	-32.37

Data presented are Mean ± SD

p-value *<0.01; **<0.001; ***<0.0001 vs base group using paried' 't" test

TABLE:17

Mean percentage Change of Lipid Parameters after Treatment with Atorvastatin in Combination with Fenofibrate on Diabetic (n=27) and Non-Diabetic Patients (n=13)



DISCUSSION

- Out of the selected 80 patients,53(66%) patients were Male and 27(34%) patients were Female.

- 4(5%) patients were in the age group of 31-40 years, 15(19%) patients were in the age group of 41-50 years, 24(30%) patients were in the age group of 51-60 years, 29(36%) patients were in the age group of 61-70 years, 8(10%) patients were in the age group of 71-80 years.

- 21(26%) patients were smoker,2(2.5%) patients were Alcoholic, 14(17.5%) patients were both Smoker and alcoholic, 15(19%) patients were smoker, alcoholic and chewer and 28(35%) patients were neither asmoker, chewer nor alcoholic.

- 29(36%) patients were vegetarian and 51(64%) patients were mixed diet.

- 29(36%) patients had only Hypertension, 16(20%) patients had only Diabetes mellitus, 23(29%) patients had both hypertension and diabetes mellitus and 12(15%) patients had no hypertension and diabetes mellitus.

- 24(30%) patients had family history of coronary artery disease and 56(70%) patients had no family history of coronary artery disease

- A total of 80 patients were enrolled in the study. They received atorvastatin (n=40) and combination of atorvastatin and fenofibrate (n=40) for a period of 6 months.After 6 months there was a significant reduction ($P < 0.0001$) in TC (16%) , TG(16.5%) , LDL-C(24%) , VLDL-C(18%) and significant increase in HDL-C in monotherapy group as compared to baseline values. There was a significant reduction ($P<0.0001$) in TG(34%) , LDL-C(26%), VLDL-C(33.5%) except TC and insignificant increase in HDL-C in combination therapy group as compared with baseline values.

- Significant changes in TG, HDL-C, LDL-C,VLDL-C were found in the combination therapy group (-34%,+25%, -26%, -33.5% respectively) versus the monotherapy group (-16.5%,

+0.6%, -24%, -18% respectively; all P<0.0001 between groups).

- There was a significant change in heart rate, systolic BP, diastolic BP, fasting blood glucose were found in the combination therapy group (-2.01%, -10.2%, -13.15%, -1.85% respectively) versus the monotherapy group (-1.07%, -9.53%, -9.25%,+1.14% respectively ; all P<0.0001 between groups).

- Both treatments were well tolerated, with no significant differences in the incidences of adverse events between the Two groups.

- The analysis revealed that Group A (monotherapy) each One patient had adverse effects ofAnthralgia,fatigue, diarrhoea, Two patients had Nausea and Three patients had Headache.

- Group B (Combination therapy) Two patients had adverse effects ofRhabdomyolosis, two patients had Anthralgia, and two patients had Diarrhoea.

- In both groups none of the patients had not had the adverse effects of Pancreatitis, Depression, Memory Loss, Confusion, Aggressive Reactions.

- There was a significant change between the male and FemalePatients on the lipid parameters in both therapies.

- In monotherapy group a total of 40 patients 27 patients were male and 13 patients were female.

- In the monotherapy group significant reduction (P < 0.0001) in TC (16%) , TG(15%) , LDL-C(22.5%) , VLDL-C(17%) in Male patients as compared to baseline values. There was a significant reduction (P<0.0001) in TC (17%), TG(19.5%) , LDL-C(27%), VLDL-C(20%) and significant increase in HDL-C in Female patients as compared with baseline values.

- Significant changes in TC, TG, HDL-C, LDL-C,VLDL-C were found in the Female patients (-17%, -19.5%, +3.1, -27%, -20% respectively) versus the male patients (-16%, -15%, -0.58, -22.5%, -17% respectively; all P<0.0001 between groups).

- In Combination therapy group a total of 40 patients 26 patients were male and 14 patients were female.

- In the Combination therapy group significant reduction (P< 0.0001) in TC (15%), TG(30%) , LDL-C(24%) , VLDL-C(29%) in Male patients as compared to baseline values. There was a significant reduction (P<0.0001) in TC (18%), TG(50%) , LDL-C(30%), VLDL-C(42%) and significant increase in HDL-C in Female patients as compared with baseline values.

- Significant changes in TC, TG, HDL-C, LDL-C,VLDL-C were found in the Female patients (-18%, -50%, +20.7, -30%, -42% respectively) versus the male patients (-15%, -30%, +28.64, 24%, -29% respectively; all P<0.0001 between groups).

- There was a significant improvement between the Diabetic and non-diabetic patients in both the therapies.

- In monotherapy group out of 40 patients 19 patients were Diabetic patients and 21 patients were Non-diabetic patients.

- In the monotherapy group significant reduction (P < 0.0001) in TC (13.4%) , TG(17.5%), LDL-C(20%) , VLDL-C(16%)and insignificant increase in HDL-C in Diabetic patients as compared to baseline values. There was a significant reduction (P<0.0001) in TC (19%), LDL-C(28%), VLDL-C20(%) except TG and insignificant decrease in HDL-C in Non-diabetic patients as compared with baseline values.

- Significant changes in TC, LDL-C,VLDL-C were found in the Non-diabetic patients (-19%, -28%, -20% respectively) versus the Diabetic patients (-13.4% , -20%, -16% respectively; all P<0.0001 between groups).The observed difference in a decrease in TG and change in HDL-C was not statistically significant between the Diabetic and Non-diabetic patients.

- In the combination therapy group out of 40 patients 27 patients were diabetic patients and 13 patients were Non-diabetic patients.

- In the Combination therapy group significant reduction ($P < 0.0001$) in TC (14%), TG(35%), HDL-C(21.6%), LDL-C(20.7%) , VLDL-C(35.8%) in Diabetic patients as compared to baseline values. There was a significant reduction ($P<0.0001$) in TC (15%), HDL-C(29%), LDL-C(28.6%) except TG and VLDL-C in Non-diabetic patients as compared with baseline values.

- Significant changes in TC, HDL-C, LDL-C, were found in the Non-diabetic patients (-15%, +29%, -28.6% respectively) versus the Diabetic patients (-14%, +21.6%, -20.7 %, respectively; all $P<0.0001$ between groups). The observed difference in a decrease in TG, VLDL-C was not statistically significant between the Diabetic and Non-diabetic patients.

CONCLUSION

- On comparing the gender-wise it was found that the improvement of lipid profile was better in case of female patients in both monotherapy and combination therapy compared to male patients.

- On comparing the diabetic and non-diabetic dyslipidemic patients it was found that the improvements of non-diabetic patients were slightly higher than that of diabetic patients in both therapies.

The therapeutic aspects of the study can be concluded as

Dyslipidemia is characterized by increased low-density lipoprotein cholesterol (LDL-C), elevated Triglycerides(TG), and decreased High-density lipoprotein cholesterol (HDL-C). It is more common in diabetes and associated with increased risk of Coronary artery disease.

- Atorvastatin therapy was effective to the patients with high level of TC, TG, LDL-C and VLDL-C.

- Patients with high level of TC, TG, LDL-C and VLDL-C and low levels of HDL-C were effectively treated with atorvastatin along with fenofibrate than the normal level.

- The combination therapy (atorvastatin along with fenofibrate) was more effective thanthat of monotherapy (atorvastatin).

- Monotherapy with statins or Fibrates may not effectively control all lipid parameters.

- The atorvastatin-fenofibratecombination had been shown to have highly beneficial effect on lipid parameters in diabetes associated with dyslipidemia.

- Both the therapies were safe.

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PROFORMA -I

INFORMED CONSENT FORM

Patient Name : Patient ID:

Age : Date :

Sex :

I was explained about the description of the research study and they have answered allthe questions I have at this time. I have been toldthat there are no risks and only benefits associated with participating in this study.

Ifreely volunteertoparticipate in this study. I understand that I need not have to take part in this study and that my refused to participate will involve no penalty. Further I understand that I am free to discontinueparticipationfromthis study at any time.

Clinician's Name : Patient's Signature :

PROFORMA- II

PATIENT DETAILS FORM

Patient Id: Patient Name:

Age: Sex:

Height: Weight:

Consultant name:-Dr.

Review on:

Diagnosis:

Complaints:

Past medical history:

Past medication history:

Social history:

Nonalcoholic/alcoholic:

Non smoker/smoker:

Vegetarian/non vegetarian:

Present medication history:

Family history:

Any other associated diseases:

PROFORMA- III

PATIENT'S LAB INVESTIGATION CHART

Patient Name : Patient ID:

Age : Date :

Sex :

Parameters	**Base line**	**Review I**
Lipid Profile		
Total Cholesterol		
Triglycerides		
HDL-C		
LDL-C		
VLDL-C		
Fasting Glucose level		
Heart Rate		
Blood Pressure		
Systolic		
Diastolic		
Renal Function Tests		
Urea		
Creatinine		

PROFORMA- IV

MEDICATION CHART

Patient Name : Patient ID:

Age : Date :

Sex :

S.No.	No.of days	Medications	Dose/ Frequency	Time	Route
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					

PROFORMA- V

ADVERSE DRUG REACTION FORM

Patient Name : Patient ID:

Age : Date :

Sex :

ADVERSE EFFECTS	**REVIEW**
Rhabdomyolysis	
Pancreatitis	
Anthralgia	
Fatigue	
Diarrhoea	
Nausea	
Headache	
Depression	
Memory Loss	
Confusion	
Aggressive Reactions	